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THE JOURNAL OF CLINICAL NUTRITION

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LACK OF AVITAMINOSIS *AMONG ALCOHOLICS:*

ITS RELATION TO FORTIFICATION OF CEREAL PRODUCTS AND THE GENERAL NUTRITIONAL STATUS OF THE POPULATION

By WILLIAM G. FIGUEROA, M.D.,* FREDERICK SARGENT, M.D.,† LOUIS IMPERIALE, M.D.,‡ GORDON R. MOREY, M.D.,§ CAMEN R. PAYNTER, M.D.,‖ LOUIS J. VORHAUS, M.D.¶

AND

ROBERT M. KARK, M.R.C.P., (LOND.), F.A.C.P.**

IN THIS COMMUNICATION we will present data which demonstrate that the enrichment of bread and flour has contributed significantly to the nutritional health of the nation. This study started somewhat fortuitously, as we had not planned to observe the effect of enrichment on the population. At the time this investigation began in 1946 we were looking for florid *primary* nutritional disease in a large general hospital in an effort to find suitable cases of beriberi for study. Unfortunately for our research program, we did not find any adult patients who were ill with beriberi or other primary deficiency syndromes. We next sought material among a large group of chronic alcoholics—a population known to be notoriously poor eaters. Our previous experience[1-3] suggested that we could expect to find florid nutritional disease in a high percentage of alcoholics. The House of

From the Medical Nutrition Laboratory, Chicago; an installation under the jurisdiction of the Surgeon General, U. S. Army; and the Department of Medicine, University of Illinois College of Medicine, Chicago, Ill.

The opinions expressed in this paper are those of the authors and do not necessarily represent those of any governmental agency.

* Resident in Medicine, Veterans Hospital, Los Angeles, Calif.; formerly Captain, Medical Corps, U. S. Army.

† Assistant Professor of Physiology, University of Illinois, Urbana, Ill.; formerly Specialist, Clinical Investigation Division, Medical Nutrition Laboratory; on military leave of absence for tour of active duty with the U.S.A.F.

‡ Resident in Pediatrics, King's County Hospital, Brooklyn, N. Y.; formerly Captain, Medical Corps, U. S. Army.

§ Resident in Medicine, Veterans Hospital, Hines, Ill.; formerly Captain, Medical Corps, U. S. Army.

‖ Fellow in Medicine, The Mayo Foundation, Rochester, Minn.; formerly Captain, Medical Corps, U. S. Army.

¶ Resident in Medicine, Research and Educational Hospitals, University of Illinois College of Medicine, Chicago, Ill.; formerly Captain, U. S. Army Medical Corps.

** Professor of Medicine, University of Illinois College of Medicine, and Attending Physician, Research and Educational Hospitals, Chicago, Ill.; formerly Assistant Director and Chief, Clinical Investigation Division, Medical Nutrition Laboratory.

Correction of the City of Chicago (known locally as the Bridewell) seemed to provide a suitable population among which we might find patients ill with beriberi. Each year the institution admits approximately 20,000 individuals, 56 per cent of whom are alcoholics. From June 1948 to July 1949, we screened nearly 16,000 inmates for evidence of the classical nutritional deficiency syndromes; we made a careful nutritional survey of 451 newly admitted inmates during the height of the "pellagra season," and we made detailed physiological and biochemical measurements in 24 alcoholics who were selected for study.[4]

To our surprise, among the three groups we found only two men ill with pellagra, only one man probably suffering from beriberi heart disease, three men with signs of florid ariboflavinosis, and one individual suffering from Wernicke's encephalopathy. There were also seven men ill with polyneuropathy, which was possibly nutritional in origin.

Methods

Subjects

The alcoholics and other derelicts in the City of Chicago are accustomed to congregate on West Madison Street, an area densely occupied by taverns, flophouses and cage hotels. The natural history of these individuals has been vividly described by Slocum.[5] A cross-section of this group of men are admitted to the House of Correction. During the period June 1, 1948 through June 30, 1949, there were 20,710 admissions. Of these men approximately 40 per cent were colored and 60 per cent white. Ninety per cent of the white males admitted were alcoholics. Only five per cent of the colored inmates were found to be alcoholics.

The typical alcoholic who is "picked up" by the police on West Madison Street is "booked" at the Desplaines Police Station, where he spends about 12 hours. After being sentenced he is taken to the House of Correction. No more than 24 hours elapse from the time of pick-up to the time of admission. Incarceration ranges between 10 days and three months. When he arrives at the institution he is registered, bathed, sprayed with liberal amounts of DDT, and dressed in prison garb.

The typical or "average" alcoholic was a bleary-eyed, dirty, smelly, unshaven, dehydrated, and unhappy man of about 45 years of age. He appeared prematurely old. He was shaking and frequently on the verge of delirium tremens. He was clothed with several layers of dirty worn-out clothes, and his body, especially his face and hands, showed evidence of recent or old trauma. He harbored lice and his skin was covered with the infected burrows of scabies. He was often edentulous or had gross dental caries. He continuously asked for some form of sedation to relieve his "nerves," and presented a picture that was indeed a far cry from the "man of distinction" depicted in present-day magazine advertisements.

Screening of Newly Admitted Inmates for Evidence of Florid Nutritional Disease

At each morning "line-up" of newly admitted prisoners they were examined rapidly for evidence of malnutrition. This screening examination was usually confined to the head, eyes, mouth and tongue, teeth and gums, skin, and extremities. In this examination we were primarily interested in identifying possible cases of beriberi heart disease, pellagra, scurvy, polyneuropathy, frank ariboflavinosis, anemia, gross edema, phrynoderma, or xerophthalmia.

Nutrition Survey

At weekly intervals from the first week in March through the first week in June 1949, a detailed nutritional survey of newly admitted inmates was conducted. This time was chosen since it represented the months of the year when florid B-complex deficiency disease is most likely to appear.[6] Each Thursday 35 men giving a history of alcoholism were chosen at random from the morning "line-up" for study. A thorough clinical examination was made of each individual. This included measurement of nude height and weight and a search for signs of malnutrition.[7,8] Each physician did not see all the patients. When malnutrition was suspected by any observer, it was the custom for all members of the team to see the patient and discuss the findings be-

fore a final diagnosis was made. Each patient was also questioned regarding his age and his intake of alcohol.

Assessment of Dietary Intake

Obtaining a reliable dietary history from an alcoholic is extremely difficult. They underestimate, or fail to recall the quality and quantity of their daily food consumption. Moreover, many of them do not give the same story to different observers. In spite of the obstacles, we felt that obtaining a dietary history might reveal some interesting information concerning their food habits. Accordingly they were questioned with regard to: the daily consumption of seven basic food groups; a typical day's food intake; the approximate daily expenditure for food; the place where the food was bought and prepared; and the use of supplementary vitamin preparations.

To evaluate further the dietary intake of these men, several field trips were made into the "Skid Row" areas of Chicago (West Madison Street and South State Street) to observe what the men actually ate and to question the restaurant workers regarding the usual foods eaten by these alcoholics.

Biochemistry

Whole blood and plasma specific gravities were measured by the method of Phillips, *et al.*[9] and the concentrations of hemoglobin, and total plasma protein and the hematocrit were calculated from appropriate nomograms. In the survey, hemoglobin concentration was determined by Sanford and Sheard's method.[10] The urinary excretion of thiamine was measured by Hennesey and Cerecedo's technique,[11] and riboflavin by Connor and Straub's method.[12] Both vitamin assays are made by photofluorometric methods, and in the analyses a Coleman photofluorometer was used.

Physiological Measurements

During the screening process 50 men were seen who had edema, or other physical signs which led us to believe that detailed study might be profitable. These were examined thoroughly and 24 men with gross edema—9 control subjects and 15 who were considered to be potentially malnourished alcoholics —volunteered as experimental subjects. They were admitted to the Bridewell hospital wards for physiological and therapeutic studies which will be reported in detail elsewhere.[8]

Results

Examination each day at the House of Correction of some 60 newly admitted inmates soon indicated that classical nutritional deficiency disease was rare. This impression was supported by our failure to find any abnormalities among the 24 alcoholics with gross edema which could with certainty be attributed to avitaminosis. Since neither of these two studies yielded statistical data on the incidence of florid nutritional deficiency disease at the House of Correction, a nutritional survey was specially planned to be carried out during the "pellagra season," during which time data were collected for statistical evaluation of malnutrition in the Bridewell population.

Nutritional Survey of 451 Newly Admitted Inmates

During the survey 451 inmates were examined. These men were chosen from 944 inmates who had been admitted to Bridewell on the days the surveys were conducted. Since 380 of the 944 inmates were colored, and since we examined principally whites, except when an alcoholic negro was found, over 75 per cent of the newly admitted white inmates were seen. This sampling is adequate and allows the calculation of the incidence of nutritional stigmata, anemia, underweight, and overweight among the white inmates at the House of Correction.

Physical Characteristics of the Men

Of the 451 men, the records of 446 were complete enough to permit statistical analysis regarding height-weight-age relationships. Thirty-seven (8.3 per cent) of the group were negroes. Table I shows the height-weight data according to decades. The criterion used for determining overweight or underweight was that the weight should be 20 pounds or more above or below the standard values given by Duncan.[13] The height-weight ratios were calculated from the formula: height in inches divided by square root of weight in pounds.

Consideration of Table I brings out the following significant points: (1) Younger men tended to be slightly taller and slightly heavier than older men. (2) The height-weight ratio varied little with age. (3) The frequency of overweight was higher among younger men than older men. In the third decade three times as many men were overweight than were

TABLE I

Physical Characteristics of 446 Alcoholics Examined at House of Correction (Men Measured without Clothing and Without Shoes)

Age in years	Number of men	Average weight *Lb.*	Average height *In.*	20 lb. overweight		20 lb. underweight		Height $\sqrt[3]{\text{Weight}}$
				No.	Per cent	No.	Per cent	
20–29	76	144	68	9	11.8	3	3.9	13
30–39	111	142	68	9	8.1	22	19.8	13
40–49	151	140	65	9	6.0	47	30.9	12.5
50–59	88	139	66	4	4.5	25	28.4	12.7
60 and over	20	138	65	1	5.0	7	35.0	12.6
All ages	446	141	66	32	7.2	104	23.2	12.9

underweight. (4) More older men are underweight than were overweight. In this sample population the average weight was 141 pounds and the average height was 66 inches. Thirty-two (7.2 per cent) men were overweight and 104 (23.2 per cent) men were underweight.

A remarkably high percentage of the alcoholics examined were underweight. A comparison of the incidence of underweight among alcoholics versus the incidence of underweight in the general population was possible through the kindness of Dr. L. I. Dublin[14] of the Metropolitan Life Insurance Company who made available to us comparable data. His data are shown in Table II and are derived from a study by Dublin, Fisk, and Kopf.[15] The criterion for underweight in that study was deviation of the actual weight from the standard weight by 20 per cent. The standard age-height-weight data for that study were based on the Medico-Actuarial Investigation of 1912, at which time the average height and weight of the population was probably less than present-day averages. When our data are compared with data on the general population, it is at once evident that, with the exception of the youngest men (20–29 years), almost ten times as many alcoholics were underweight as were underweight in the general population.

TABLE II

Comparison of Data on Age Distribution of Per Cent of Chronic Alcoholic Men Underweight at Bridewell with Data on Policy Holders of Metropolitan Life Insurance Company (Dublin, 1949)

Data from Bridewell		Data from Dublin (1949)	
Age in years	Per cent of men underweight	Age in years	Per cent of men underweight
20–29	3.9	Under 25	2.0
30–39	19.8	25–34	3.2
40–49	30.9	35–44	2.3
50–59	28.4	45–54	1.5
60 and over	35.0	55 and over	2.1
All ages	23.2	All ages	2.4

Presence of Physical Stigmata Suggestive of Malnutrition

A large number of different minor and major physical changes on the surface of the body and easily visualized mucous membranes have been described in the literature as being pathognomonic signs of various types of malnutrition. Below are recorded, in brief, the incidence of a large number of these physical findings.*

Skin. Lesions of the skin were frequently noted. The outstanding findings were filth and scabies but there were noted perifollicular hyperkeratosis, 44 cases; acneform eruption, 32 cases; "wine sores" or Vagabond's disease,† 6 cases; symmetrical dermatitis of the exposed parts, 5 cases; seborrhea of the face, 5 cases; atrophy of the skin, 4 cases; perineal skin changes, 2 cases; and unequivocal evidence of previous pellagrous lesions, 2 cases. One man had a scaly dermatitis of the lower legs.

* The observations are detailed in Tables XV, XVI and XIX of our monograph.[16]

† "Wine sores" is the name given by alcoholics at Bridewell to multiple circular ulcerative infected lesions of the lower extremities. These have sharp edges and a sloughing base. When they are present the legs are often edematous. The lesions occurred

Among these various lesions, those frequently associated with malnutrition are perifollicular hyperkeratosis, symmetrical dermatitis of the exposed parts, and seborrhea of the face. What are some of the characteristics of these lesions as seen among this group of alcoholics? Among the 44 men with perifollicular hyperkeratosis the lesions tended to occur most frequently on the lower extremities and in areas subject to environmental trauma —buttocks, thighs, knees, calves, and about the abdomen. The severity of the lesions varied from mild to marked. In few cases was the distribution widespread in any individual. There were five patients in whom symmetrical dermatitis of the exposed parts was noted. In only one individual, however, was such a lesion observed in whom a number of other concurrent signs consistent with malnutrition made it possible that malnutrition was the basis for the dermatitis. The lesions in the other patients either had a vascular origin or their cause could not be determined since the dermatitis was an isolated finding.

One of the noteworthy observations of this survey was the scarcity of lesions suggestive of pellagrous dermatitis. The survey was conducted during the time of year when pellagra was most likely to occur. Indeed, we saw many men with sunburned faces, necks, arms, and trunks, yet no men ill with unequivocal pellagra were seen, and we observed only one patient whose skin lesions were suggestive of florid pellagra.

Eyes. The following eye findings were noted: conjunctival injection, 20 cases; pingueculae, 8 cases; limbal vascularity, 3 cases; corneal opacities, 2 cases; and pterygium, 2 cases. One man had blepharitis, loss of eyelashes, conjunctivitis, and photophobia. There were no cases of blepharospasm, conjunctival dryness, or Bitot's spots.

Lips. Ten men had cheilosis and angular stomatitis. Sixteen had angular scars. In the majority these lesions were minimal.

Cheilosis and angular stomatitis have been termed non-specific nutritional stigmata, principally because these lesions frequently occur in association with adentia, false teeth, and infection.[17,18] Our experience does not indicate such a close relationship. For example, among 51 men having no teeth and no dental plates, only 3 had angular lesions. Among 22 men having plates, there were only 3 having an associated angular lesion.

Teeth and Gums. Of these 451 men, 141 had dental caries, 40 had pyorrhea, 24 had gingivitis, 3 had red gums and one had retraction of gums. Seventy-three men were edentulous and 22 had plates—either upper, lower, or both. Six of the men had bleeding gums.

Tongue. The following physical signs of the tongue were seen: tooth markings, 23 cases; red tongue, 12 cases; papillary atrophy, 11 cases; fissured tongue, 9 cases; patchy denuded areas of epithelium, 4 cases; pale tongue, 2 cases; and edema of tongue, 1 case. Two "scrotal" tongues were also observed. In only seven men, however, was there any association of glossal signs one with another. Five men had red tongues with papillary atrophy, one man had a red, fissured tongue, and one man had a pale tongue with tooth markings. The association between glossal and lip lesions was even less frequent. Two men had red atrophic tongues, cheilosis, and angular stomatitis. One man had tooth markings and angular scars, and one man had cheilosis, angular stomatitis, and a fissured tongue, the color of which was normal.

Buccal Mucosa. No gross abnormalities of the buccal mucosa were noted among the inmates.

Cardiovascular Findings. Among the 451 men, 45 men were found to have varicose veins. Six had edema of the lower extremities. Two of the men with edema were ill with cardiac failure and 2 had varicose veins. One man

in men whose personal hygiene was poor. Cultures of the lesions were made but no unusual organisms were found. The lesions healed in two to three weeks after treatment with furacin and the residual scars were pigmented and indurated. We have been unable to find a description of these lesions in the literature. The active lesions remind us of "desert sores" seen in North Africa. The healed lesions seem to be the same as "Vagabond's Disease." As far as we can tell, these wine sores bear no relation whatsoever to the nutritional status of the alcoholic. They seem to be related to personal habits and foul clothing.

with varicosities also had several small infected burns on one leg. The other appeared well-nourished, but in him ankle jerks could not be elicited. The sixth man (71 years old) was thin and showed evidence of recent weight loss. There were red scaly lesions on the lower extremities and feet became dusky red when dependent. An open chronic ulcer was present on the right hallux and the ankle jerk could not be elicited on the left side. The dorsalis pedis and posterior tibial pulses were present and there were no varicosities. This man might have had a nutritional disturbance.

Liver. The liver was palpated in 16 men. In three men, although the liver was palpable, it was not considered to have been enlarged. In six of the remaining 13 men, there were no other associated stigmata of malnutrition. Among the remaining seven cases there were isolated findings such as pyorrhea and thickened skin across instep; patchy denuded tongue; atrophy of skin and absent ankle jerks; obesity; and tooth markings. For the most part, the alcoholics who had enlarged livers appeared clinically well-developed and well-nourished. Other clinical evidence of disturbance of liver function such as icterus, jaundice, telangiectasia, and palmar erythema were conspicuous by their absence.

The only men in whom palmar erythema was noted were two in whom the liver was not felt, and who showed no other stigmata of liver disease.

Neurological Disturbances. The following neurological disturbances were noted: loss of ankle jerk, 18 cases; hyperactive reflexes, 11 cases; loss of vibratory sense, 5 cases; calf tenderness, 3 cases; and loss of knee jerk, 2 cases. One man complained of burning feet. In only 4 of these men was it possible to associate two or more neurological signs. Although the men had objective neurological signs consistent with early neuropathy, it is most interesting, and significant, that subjective complaints referable to the nervous system were lacking. Hyperactive reflexes were recorded in 11 instances. In the majority of these a recent bout of drinking was the probable cause of the overactivity.

TABLE III
Frequency Distribution of Hemoglobin Levels Among 380 Newly Admitted Alcoholics

Hemoglobin	Total group	
	No. of men	Per cent
Gm./100 ml.		
10–10.9	3	0.8
11–11.9	7	1.8
12–12.9	25	6.6
13–13.9	35	9.2
14–14.9	102	26.8
15–15.9	74	19.5
16–16.9	66	17.3
17–17.9	49	12.9
18–18.9	17	4.5
19–19.9	2	0.6
TOTAL	380	100.0
MEAN	15.2	

Hemoglobin Determinations. The hemoglobin concentration was determined in 380 of the 451 alcoholics. The colorimetric method of Sanford and Sheard[10] was used. The results are summarized in Table III. The mean concentration of hemoglobin was 15.2 Gm./100 ml., and the majority of the values tended to fall within "normal ranges" given for normal adult males: 14.5 to 16.9 Gm./100 ml.[19] In these alcoholics 63.9 per cent of the men had hemoglobin concentrations between 14.0 and 16.9 Gm./100 ml. There was no significant correlation between concentration of hemoglobin and physical stigmata of malnutrition or excessive underweight and overweight.

The finding that almost two-thirds of the alcoholics had "normal" hemoglobin levels is remarkable when we recall the natural history of the alcoholic. One observation, however, casts some doubt on these hemoglobin values as representing the true picture: the frequent occurrence of concentrations in excess of 17 Gm./100 ml. Dehydration was suspected, and ten alcoholics who had high hemoglobin levels were selected for study. Determination of hemoglobin was repeated on the first and second days following the nutritional survey. Initial hemoglobins ranged from 16.1 to 19.6 Gm./100 ml. In one day the hemoglobin decreased by an average of 1.2 Gm./100 ml. (0.2–2.6 Gm./100 ml.). In the absence of bleeding or hemolysis, such rapid changes

can only be attributed to hydration of the blood and tissues.

The fact that the hemoglobin values may have been biased by dehydration makes it impossible to estimate exactly the true incidence of anemia among the group surveyed. No man had a hemoglobin content of less than 10 Gm./100 ml., and only 3 of the 380 alcoholics had values between 10.0 and 10.9 Gm./100 ml. Clinical observations show that anemia was rare. Only one case of marked pallor was noted among 451 men examined. Allowing for dehydration, certainly not more than 10 men would have shown hemoglobin levels below 10 Gm./100 ml.

Clinical Impressions of the Physical Status of the Alcoholics Examined at the House of Correction

The records of the 451 alcoholics examined in the nutritional survey were critically reviewed and appraised. A decision was made on clinical grounds as to whether the man might be judged to have probable avitaminosis and unequivocal avitaminosis. Of the 451 men, 26 (5.6 per cent) were judged to be probably avitaminotic. Only 10 (2.2 per cent) were judged to be unequivocally avitaminotic. Among these 10 alcoholics, all of whom were white, there were no clear-cut instances of florid nutritional deficiency disease, such as scurvy, pellagra, beriberi, or avitaminosis A. There were 4 men whose findings suggested nutritional polyneuropathy and 2 men who probably had ariboflavinosis. One of the subjects with polyneuropathy had a marked iron deficiency anemia.

Whereas only 2.2 per cent of the 451 inmates were judged to have clinical avitaminosis, 23.2 per cent of the same group were certainly in caloric deficiency. These men were 20 pounds or more under the standard weight.

Further Observations and Discussion

Alcoholism and Malnutrition

Since 1933, when Minot, Strauss, and Cobb[20] indicated that a deficient diet was responsible for "alcoholic" polyneuritis, the concept that malnutrition and avitaminoses are common among alcoholics has become firmly established in the literature of nutrition and in the minds of physicians. Weiss and Wilkins,[21] for instance, reported that beriberi heart disease occurred once in every 160 medical admissions to the Boston City Hospital. Since the admission rate of alcoholics was not stated, one cannot accurately judge from this study the incidence of beriberi heart disease among alcoholics. The incidence of polyneuropathy among alcoholics is equally uncertain, but, according to Jolliffe,[22] it may be as high as 20 per cent among alcoholics admitted to Bellevue Hospital in New York City. At the time (1942) he published his observations, Jolliffe expressed the opinion that this incidence was beginning to decline perceptibly. In 1941, Harris and Harris[23] estimated that there were about 20,000 cases of alcoholic pellagra in the United States and stated that the incidence of this disease and of alcoholic cirrhosis of the liver were on the increase because of the increased consumption of alcoholic beverages. Other investigators[24,25] have reported large series of patients with alcoholic pellagra, but in neither of these reports is there any information concerning the incidence of alcoholic pellagra among general hospital admissions or among alcoholics admitted to the hospital. Texon,[26] on the other hand, has reported that vitamin deficiencies occurred in only about 10 per cent of 200 alcoholics admitted to a general hospital. In contrast, he believed that 65 per cent of the group he studied had "fatty livers."

If malnutrition is as common in this country as some claim,[27,28] and if we accept the above statistics, then clinical malnutrition and specific avitaminosis should be very common among alcoholics. This of course raises the question: why were we unable to find frank nutritional syndromes among 16,000 inmates of Chicago's City Jail, many of whom were alcoholics?

Factors Producing Nutritional Syndromes in Alcoholics

The explanation usually offered for the high incidence of alcoholic pellagra and alcoholic polyneuritis among alcoholics is that alcohol requires B-complex vitamins,[22] especially thia-

mine, for its metabolism in the body. Recent evidence indicates, however, that alcohol may not require thiamine for its metabolism. The most convincing data for this fact has been presented by Berg, Stotz, and Westerfeld[29] and Westerfeld and Doisey.[30] Their observations have been summarized and presented in a simple manner by Moore.[31] In fact, Butler and Sarett[32] concluded from their experiments that alcohol might actually spare thiamine. It is evident, therefore, that either other members of the B-complex may play a major role in the metabolism of alcohol as suggested by Meiklejohn[33] and Strauss[34] or that we must look to other mechanisms or conditioning factors which might precipitate nutritional syndromes in the alcoholic. There are, as far as we know, no data to support the concept that antimetabolites are present in beer, wine, or other spiritous liquors—nor that aldehydes or other metabolic breakdown products of alcohol are, *per se*, protoplasmic poisons.

The alcoholic, besides eating a low caloric, low protein diet, is continuously exposed to both inclement weather and to man's inclemency. His dirty habits and dirty environment subject him to continual chronic infection of the skin and repeated bouts of alimentary disorders. These factors must certainly influence his nutritional status.

Evidence from the study of anorexia nervosa and from population groups studied in Europe during World War II whose diet, save for excess alcoholic intake, was similar in many ways to that of the alcoholic, indicates that the stigmata of avitaminosis were not common among them. Therefore, the inadequate food intake of the alcoholic probably is not the *prime* cause of vitamin deficiency disease in such an individual. If he comes down with one of the florid nutritional syndromes, it must be the result, in the main, of conditioning factors. What these factors are we will attempt to indicate later in the paper. That pellagra, beriberi, and other similar diseases are associated with chronic alcoholism, we do not deny. In fact, in 1939 and 1940 these diseases were common enough among the alcoholics in Boston so that one of us (R. M. K.) was accustomed in the spring to satisfy his scientific needs by finding alcoholic pellagrins on the benches of Franklin Park whenever he needed to admit one to the hospital for study. Many others have had similar experiences.

Correlations of Dietary Intake, Physical Signs, and Biochemical Observations in the Bridewell Alcoholics

The Diet of the Alcoholic. Two types of dietary histories were obtained from the alcoholics studied at the House of Correction. By use of the formal history, as outlined above in "Methods," an attempt was made to elicit information regarding the kind and frequency of the different foods eaten, the amount of money spent for food, and the consumption of alcohol. This formal history proved to be quite unreliable. In contrast, informal histories were obtained by engaging various alcoholic inmates in conversation and then offhandedly discussing their consumption of food and alcohol. From such histories we learned that these men ate large quantities of bread (some men claiming to have eaten half a loaf a day), some hash, or stew, coffee and doughnuts, and occasionally sandwiches or spaghetti. Our field experience in West Madison Street and South State Street substantiated these statements. The impressions we obtained from informal conversation, together with observations in West Madison Street and South State Street, agree with those of others[20] and demonstrate that the alcoholics of Chicago do not eat much differently from the alcoholics of the depression years. Although their food pattern may be similar qualitatively when consumption of various foods during the years of depression is compared with modern times, there have been important quantitative changes in the composition of some of the foods. These have contributed significantly to the nutritional status of the alcoholics at the House of Correction.

Physical Signs of Malnutrition

Although florid nutritional deficiency disease was quite uncommon, a large number of the alcoholics presented various signs which have been attributed to malnutrition. Table IV shows the frequency with which abnormali-

TABLE IV

Incidence of Physical Signs Suggestive of Malnutrition Observed Among Inmates at House of Correction

Abnormality	Number of times observed	
	50 selected alcoholics	451 newly admitted inmates
Tongue*	39	42
Lips	5	26
Gums	0	67
Skin	15	112
Nervous system†	22	28

* Does not include tooth markings, a sign which we consider worthless as an indicator of nutritional status (see text).

† Does not include hyperactive reflexes.

ties of the tongue, lips, gums, skin, and nervous system occurred among 501 inmates given thorough physical examinations. Consideration of this table brings out certain facts. Among 451 newly admitted inmates who were chosen at random, by far the most common abnormalities were those of the skin. A relatively smaller number of the men had abnormalities of the tongue, lips, gums, and nervous system. Among 50 alcoholics who were selected for detailed and serial studies which are reported elsewhere,[4] the most commonly observed abnormalities were those of the tongue and nervous system. The reason for this distribution was that the tongue changes and disturbances of the nervous system were used as criteria for selection because of their reported significance as early signs of malnutrition.

Because this second group represents a highly selected population, the data from the first group must be used in estimating the frequency with which physical signs occur among alcoholics. Tongue changes, such as papillary atrophy, hypertrophic papillae, redness, and pallor, are among the most reliable and earliest indicators of malnutrition.[35-37] We strongly question, however, the nutritional significance of tooth markings of the tongue—a sign which occurred 23 times among the newly admitted inmates. Although "tooth markings" is supposed to be a very early sign of deficiency of niacin,[7,18] we were greatly impressed by the fact that tooth markings occurred in about one-third of the healthy negroes seen in the daily line-up for medical inspection. These negroes presented absolutely no clinical evidence of malnutrition and the great majority (95 per cent) were not alcoholics. Tooth markings were also frequently seen among clinically well-nourished whites. Common clinical accompaniments of tooth markings in both white and colored individuals were widely separated teeth and/or malocclusion. Furthermore, in a number of individuals given a therapeutic test, this "lesion" failed to respond to large doses of niacinamide, even when therapy was continued for as long as one month. Of the other tongue changes of unequivocal significance we estimate that they occurred in about 10 per cent of the inmates examined.

Abnormalities of the nervous system occurred 28 times among the 451 newly admitted inmates. In the majority these signs occurred as isolated findings, the most frequent being absence of ankle jerks or hypoactive reflexes. The latter finding was accredited with no nutritional significance, for this finding is not infrequent in the case of older individuals.[38] In only 4 men did signs group themselves in such a way as to suggest the presence of polyneuropathy. Thus, probably not more than 1 per cent of the newly admitted inmates had polyneuropathy.

Lip changes were seen infrequently. Of the 26 times that such changes were observed, 10 men were considered to have cheilosis and the remainder had angular scars. Only one individual of the 451 inmates and 2 of the 50 alcoholics were considered to have had frank ariboflavinosis.

Lesions of the gums were seen 67 times in the survey. Because of the high incidence of severe dental caries and infection of the gums, signs indicative of dental neglect, nutritional assessment of the lesions of the gums was difficult. In fact, we hesitate to attach any nutritional significance at all to the presence of these lesions.

Far and away the most frequent abnormalities seen were various lesions of the skin. The non-specificity of the various dermal lesions is well known.[39] Lack of bodily care (infrequent bathing and change of clothing), exposure to

inclement weather, excessive trauma, chronic irritation by clothing, chronic low grade infection, and occupational exposure make such lesions as follicular hyperkeratosis, thickened skin across the instep, "wine sores" (Vagabond's disease), acne rosacea, and seborrhea of dubious nutritional origin.

The fact that we observed few cases of symmetrical dermatitis of exposed parts is especially noteworthy. Only one man of the 451 newly admitted inmates was considered to have had dermal lesions even suggestive of pellagra. Certainly at this time of the year we should have seen more pellagra if the nutritional intake of the men had been sufficiently poor or unbalanced to permit its development, especially since so many of the men had been exposed to sunlight.

Ocular abnormalities were uncommon among the 451 inmates. Most of the changes that were seen occurred among individuals who had recently been drinking heavily. The typical "rheumy" eye of the alcoholic was the most common abnormality.

Beriberi Heart Disease and Other Cardiovascular Abnormalities Seen in Alcoholic Patients

From a review of the American literature on the cardiovascular manifestations of malnutrition one would conclude that beriberi heart disease would be commonly found in a group of alcoholic patients of the type reported here. Yet after specifically looking for this entity for a period of over one year, and after seeing many thousands of alcoholics, we were unable to find any clear-cut cases of beriberi heart disease.

In point of fact, during five years in Chicago we have found only two clear cases of beriberi heart disease with failure.

Sutton[40] also failed to find any cases of this condition in a study of similar nature which was undertaken in Cook County Hospital.

Blankenhorn[41] writes that during 1945–49 ". . . there have been but three patients on the medical service diagnosed beriberi heart disease. This medical service admitted 9000 patients in that time. . . ."

Underweight: Protein versus Caloric Deficiency

The outstanding physical finding on the alcoholics studied at the House of Correction was the high incidence of "underweight." Among the 24 specially selected alcoholics, 39 per cent weighed less than standard weight by 20 pounds or more. Among the 451 newly admitted inmates chosen at random, 23 per cent weighed less than the standard weight by 20 pounds or more. These percentages of underweight are several times higher than those of underweight among representative normal male populations. This finding strongly suggests that about one third of the alcoholics examined were certainly suffering from a "caloric deficiency."

We judge from our studies of the dietary intake of the average alcoholic at the House of Correction that the average daily consumption of protein was about 30 Gm. per day. On the basis of our experience with alcoholics ill with cirrhosis of the liver studied on a metabolic ward,[42] we postulate that a considerable number of underweight alcoholics, and probably some of the euweight alcoholics, were suffering from depletion of tissue protein. In the cirrhotic alcoholics of Morey *et al.*,[42] severe tissue depletion of protein coexisted with normal values for total circulating plasma protein. It is not unreasonable, therefore, to suggest that the Bridewell alcoholics were suffering from depletion of tissue protein even though their plasma protein values fell within the normal range. By virtue of the large alcoholic consumption by these individuals (we estimate that the consumption of wine and other beverages supplied between 2000 and 10,000 calories per man per day*), we must logically argue that the high incidence of underweight actually represented a loss of protoplasm by reason of long continued negative nitrogen balance rather than the usual type of caloric deficiency. This conclusion would be strengthened if it were shown that alcohol was not a "nitrogen-sparer." Although the subject of the influence of alcohol on nitrogen metabolism

* Since the maximal possible daily consumption of alcohol has been shown to be one quart of 100 proof liquor,[46] these figures are not unreasonable.

is quite controversial,[43] and although some investigators have been unable to find any significant alterations in nitrogen metabolism,[32,44] others[45] have observed a small nitrogen-sparing effect when moderate amounts of alcohol were used. On the other hand, when intoxicating doses were given, nitrogen balance became negative.[45] It is possible that the alcoholics we observed had been in negative nitrogen balance (1) because of their poor diet and (2) by reason of the consumption of intoxicating amounts of alcohol. Since the overall caloric intake from food plus alcoholic beverages should have been sufficient to maintain normal weight in the average alcoholic, we tend to accept the report that excessive alcohol has a noxious influence on tissue protein catabolism or anabolism.

Anemia

With regard to anemia, our data showed an average hemoglobin of 15.2 Gm./100 ml. Even if it is argued that the men were dehydrated when they were examined, on the basis of our data, one would not expect the hemoglobin values, on the average, to drop with rehydration by more than 2 Gm. If this happened, we would still find good levels of hemoglobin in the majority of such a group of men. We then must conclude that anemia and a deficiency of iron or other hematopoietic factors was uncommon. In fact in only 10 men out of 380 were hemoglobin values found to be below 12.0 Gm./100 ml. This finding is especially interesting in view of the fact that many of the men repeatedly sold blood to blood banks, so that they could buy more alcohol.

Fasting Hour Excretion of Thiamine and Riboflavin

Although many investigators[8] claim that the fasting hour excretion of thiamine and riboflavin are indicative of nutritional status with regard to thiamine and riboflavin, there is considerable disagreement concerning the excretory level of the vitamins which definitely indicates deficiency. This disagreement has arisen because different investigators define deficiency differently and because of wide individual variability in excretion of vitamins by individuals maintained on constant intakes of the various nutrients. This individual variability is even more marked when samples of normal populations are tested.[47] Most investigators, however, agree that on a deficient diet the urinary excretions of thiamine and riboflavin fall rapidly to very low levels. This low level may be maintained for some time before deficiency symptoms appear, and it is only after the output becomes zero that symptoms develop. For the purposes of this discussion, we define unsaturation after Johnson, Sargent, Robinson, and Consolazio;[48] viz., a urinary excretion of less than 0.6 μg./hr. thiamine and 20 μg./hr. riboflavin. Zero excretion of these vitamins is considered as constituting definite chemical evidence of severe deficiency.[49]

According to these criteria, none of the alcoholics examined were unsaturated with respect to thiamine, and only two were unsaturated with respect to riboflavin. There were no consistent correlations between low fasting hour excretions of thiamine and riboflavin and the presence of clinical malnutrition when data from individuals were compared. On the other hand, when the *average* thiamine excretion by a group of clinically malnourished alcoholics (Table V) was compared with the *average* excretion by a group of alcoholics who did not appear malnourished, there was a significantly lower fasting hour excretion by the former group.

The diagnosis of a well-developed nutritional syndrome is an easy matter, but the diagnosis of borderline deficiency states is difficult indeed.[8] There are no generally accepted criteria for the identification of these states. Many of the physical signs are nonspecific. Individual examiners differ in their interpretation of minimal lesions.[50] Chemical tests, as we have already indicated, yield variable data. Little or no correlation can be found between recent food intake and clinical evidence of malnutrition. On the other hand, there does seem to be some correlation between recent food intake and plasma vitamin levels,[51,52] urinary excretion of vitamins,[53] and the response to loading tests.[8] In some cases the diagnosis of borderline deficiency

TABLE V

Fasting Hour Urinary Excretion of Thiamine and Riboflavin by 21 Selected Alcoholics Before and After Administration of Supplementary Thiamine

Groups	Thiamine		Riboflavin	
	Mean	Range	Mean	Range
	μg./hr.		μg./hr.	
Admission				
Control*	7.5 (8)‡	1.7–20	67 (8)	36–95
P.M.A.†	2.9 (13)	0.7–6.3	70 (11)	1.7–164
TOTAL	4.7	.....	69	.....
After 12–19 days with no supplementary thiamine				
Control*	5.9 (5)	1.5–16.0	70 (5)	46–137
P.M.A.†	6.6 (4)	1.8–16.0	58 (4)	6.3–133
TOTAL	6.2	.....	65	.....
After 7–15 days of supplementary thiamine				
Control*	194 (3)	15–476	55 (3)	6.6–131
P.M.A.†	73 (6)	14–176	55 (5)	28–98
TOTAL	113	.....	55	.....

* Control group consists of alcoholics in whom there was no evidence of malnutrition.

† P.M.A. group consists of inmates who were considered to be potentially malnourished alcoholics.

‡ Number in parentheses indicates number of men from whom specimens were obtained.

states can be made when there is a history of poor diet, physical signs consistent with malnutrition, and definite evidence of chemical unsaturation.[8,48] A therapeutic response to specific treatment may confirm such a diagnosis. The diagnosis can be made with certainty if the deficiency disease recurs when the specific agent is withdrawn and if the patient responds a second time to specific therapy.

In our studies at the House of Correction it was difficult to apply therapeutic testing as an aid in diagnosing borderline deficiency. Therapeutic tests were run on a few men (Table V) whose environment had changed greatly on the day of their commitment to the institution. The men were given clean clothes to wear. They got much needed rest and sleep. Their use of alcoholic beverages had to stop. Dehydration was corrected, and they were given a good diet. These factors undoubtedly played an important role in the clinical improvement we noted both in men given therapeutic tests and in those given placebos.

Data and Speculations Regarding Various Factors Which Might Contribute to the Low Incidence of Avitaminosis Among Alcoholics of Chicago

The alcoholics incarcerated in the Bridewell are the one population group in the City of Chicago who, for most of the year, live on meals which provide little variety and which contain only small quantities of the "protective foods" recommended by the Food and Nutrition Board[54] and other experts. Yet their nutritional status with regard to vitamins was surprisingly good. There are many factors which may be responsible in whole or in part for this surprising lack of avitaminosis. Among these factors the following come to mind: (1) drinking habits, (2) economic status, (3) increased consumption of vitamins, (4) nutrition education, and (5) fortification of flour and bread.

1. Drinking Habits. Slocum[5] has described in detail the drinking habits of the alcoholic. In brief, they consume large quantities of

wines fortified with sugar and spiritous liquor, if available, as well as other toxic agents, such as "Sterno." It is possible that, at present, because of improved economic circumstances less "Sterno" and other similar substances are consumed. For example, in one year at the House of Correction not a single instance of methyl alcohol poisoning was seen. At present, the manufacturers of beers, wines, and spirits do not fortify their products with vitamins; and so far as we have been able to find out, the art and science of the manufacture of spiritous beverages has not changed perceptibly in the past ten years. It is possible that the chronic alcoholic in 1948–49 had more money to spend on liquor than he had in 1939, and he may have purchased "better" brands. Whether or not he is drinking more is difficult to say. Jellinek[55] has discussed at length recent trends in alcohol consumption in the United States. According to him the consumption of alcohol increased in the period 1938 to 1945, but the increase was principally attributable to an increase in the number of individuals drinking rather than to an increase in alcohol consumption by the individual drinker. The increase has been principally in the consumption of beer. The use of distilled spirits has actually decreased. In connection with our remarks below concerning the similarities of alcoholics in Boston, New York, Cleveland, and Chicago, Jellinek[55] presents supporting data. The per capita consumption of various types of alcoholic beverages and the total consumption of alcoholic beverages were quite similar during 1940 to 1945 in the states of Massachusetts, New York, Ohio, and Illinois; and the incidence of chronic alcoholism in the four cities was almost identical: 1251, 1023, 1007, and 1097 chronic alcoholics per 100,000 persons (ages 20 and over), respectively, for the year 1940.

2. Economic Status. The general standards of living of individuals and families in the United States have improved considerably since the depression (1929–38). Consequently, across the nation, much more money has been and is available for the purchase of food, especially the relatively expensive "protective foodstuffs": meat, milk, and eggs. There can, therefore, be no doubt that on this basis alone one may argue that the general standards of nutrition must be at a higher level now than in 1938. This is borne out by Phipard and Stiebeling's[56] observations, which show an increased consumption of food on a per capita basis and an increase in the amount of money spent on food. As far as the population of the House of Correction is concerned, it would be easy to dismiss the finding of a low incidence of malnutrition on the basis that there has been a general economic improvement in the alcoholic populations of Chicago; and that with this there has been a general improvement in their food intake, which has been reflected by improved nutritional status. We doubt that this is true. We have described above the improvident status of the Bridewell alcoholics with regard to the state of clothing, footgear, and appearance at the time of admission to the House of Correction. We have observed the food which they are accustomed to eat and find it no different in appearance and quantity from that consumed by the prewar Boston alcoholics. We believe that, even if their economic status had been improved by higher wages being paid to them when they were working and by increased generosity of the public at times when they were "panhandling," the extra money would not have been spent on the proverbial "cup of coffee" but rather on more or "better" liquor.

3. Consumption of Vitamin Concentrates and Synthetic Vitamins. Since 1938, when synthetic thiamine was first produced commercially, the manufacture and sale of B-complex vitamins as pills, capsules, or elixirs has increased steadily. At present, millions of pounds of these substances are made and sold each year.[57] (Table VI.) They are used in large part by two groups of people: those who have enough money to buy vitamin preparations for use without a physician's prescription, and those who are ordered to take such preparations by their physicians. Certainly the alcoholic is not wealthy enough to buy vitamins regularly, nor would he do so even if he had the money. Few of them see a physician except when admitted to the Bridewell, and it has never been the custom of this institution

TABLE VI

Production and Manufacturers' Sales of Thiamine, Niacin, Riboflavin, and Ascorbic Acid, 1938 to 1948 (Weirich, 1949)

Year	Thiamine production	Niacin production	Riboflavin production	Ascorbic acid production
	Lb.	*Lb.*	*Lb.*	*Lb.*
1938	.....	.....	.....	8,693
1939	.....	.....	.....	15,654
1940	.....	3,791	.....	33,373
1941	.....	143,000	3,000	92,000
1942	.....	290,000	16,000	260,000
1943	.....	163,000	72,000	763,000
1944	84,600	939,700	4,200	1,177,200
1945	169,700	958,300	68,900	1,307,100
1946	185,300	1,000,800	44,600	727,500
1947	166,409	1,076,223	.....	489,328
1948	189,727	1,048,107	.....	955,767

Year	Sales	Sales	Sales	Sales
	Dollars	*Dollars*	*Dollars*	*Dollars*
1938	.....	.....	.....	.....
1939	.....	.....	.....	707,844
1940	.....	68,085	.....	850,315
1941	.....	1,393,000	1,664,000	2,513,000
1942	.....	1,588,000	5,569,000	4,930,000
1943	.....	1,372,000	11,514,000	13,709,000
1944	6,293,700	3,007,800	1,337,300	13,192,700
1945	11,899,900	2,571,200	5,463,400	12,091,800
1946	12,984,100	3,433,600	2,938,200	9,577,400
1947	.....	.....	.....	.....
1948	.....	.....	.....	.....

to supply them with vitamins. Only one alcoholic was found who claimed that he had received vitamin preparations from his doctor.

4. Nutrition Education. In the past decade a great deal of time and money has been spent in the dissemination of facts relating to adequate nutrition and the means for attaining it. It is obvious that this propaganda has had no effect on the food habits of the alcoholic.

5. Fortification of Bread and Flour. A strong probability exists that the fortification of flours and breads with B-complex vitamins and skimmed milk powder has had a beneficial effect in preventing the development of B-complex deficiency syndromes and manifest avitaminosis in the Chicago alcoholic.

Twelve years ago, in 1940, the Food and Nutrition Board of the National Research Council endorsed the concept of fortification of flour and bread with natural and synthetic nutrients.[58] In 1941 the so-called "enrichment program" was inaugurated as a defense measure. This was done with the object of improving the health of the nation; for the introduction of steam-driven roller flour mills, in 1873, had provided the people of the U.S.A. with a uniform degerminated white flour from wheat which was nutritionally inferior to whole-wheat grist-milled flour.[59] From a nutritional point of view it might have been better, in 1940, to have endorsed a return to the production of natural whole-wheat flour, or to have endorsed the milling of a high extraction flour (as was done in Canada and Great Britain). Unfortunately, during the emergency, this could not be done in the United States.

By May 1941, about 30 per cent of the output of white bread and flour in the U.S.A. was enriched with yeast as a voluntary practice of bakers and millers. By late 1942, 80 per cent of cereal products were enriched. In January 1943, the enrichment of bread program of the

Food and Nutrition Board was aided by a war food order which made fortification of bread mandatory across the nation.

Since the war few bakers have returned to the manufacture of unenriched breads[60] and, at the time of writing, the American Institute of Baking[61] estimates that 85 per cent of all bread sold in the U.S.A. is enriched, although only 27 states have enacted laws demanding the fortification of breads and flours with vitamins and iron. In addition, degerminated corn meal and corn meal products, sold in the Southern States, are now nearly all enriched.[62]

At present, there is no law in Illinois which demands fortification of breads and flours with vitamins. Nevertheless, as a result of a canvass of all the large bakeries in Chicago and of many of the small bakeries, we estimate that over 90 per cent of all breads and flours consumed in the City of Chicago are fortified. Moreover, the large Chicago bakeries inform us that they have practiced enrichment with vitamins or vitamin concentrates since early in 1941. Data on the vitamin content of fortified bread shows on an average 11.6 mg. of niacin, 1.40 mg. of thiamine, and 0.98 mg. of riboflavin per pound weight of bread (as eaten).[63] As far as we have been able to find out, most of the bread consumed in the eating houses of West Madison and South State Street, which we surveyed and canvassed, was purchased from three large mass production bakeries in Chicago. The flour used in cooking and especially in thickening stews and soups was also fortified.

Our "average alcoholic" lives on coffee, doughnuts, bread, thick soups, spaghetti, stews, and hash. Many of them eat at least eight slices of bread a day. This would supply them with 5.3 mg. of niacin, 0.7 mg. of thiamine, and 0.5 mg. of riboflavin. To this may be added other quantities of B-complex vitamins which they obtained from their staple foodstuffs. *We believe that the food they eat, at present, supplies a sufficient quantity of B-complex vitamins to prevent florid nutritional deficiency diseases and manifest avitaminotic states.* The only difference quantitatively and qualitatively between the food eaten by the present-day alcoholic (who is free from avitaminosis) and the prewar alcoholic (who had vitamin deficiencies) is that the flour and breads are fortified. In fact, some alcoholics had a surprisingly high output of thiamine in their urine when they were admitted to the Bridewell (Table V). This indicates the level of thiamine intake from the diet prior to admission. Consumption of a good diet in the Bridewell (for from 12 to 19 days) did not change the excretion of urinary thiamine significantly (Table VII). Therefore, it is likely that fortification has been the main factor in preventing the development of deficiency states in these alcoholics.

TABLE VII

Influence of Diet of House of Correction on Urinary Excretion of Thiamine by Nine Alcoholics*

Case	Initial thiamine excretion	Interval with no supplementation	Final thiamine excretion
	μg./hr.	*Days*	*μg./hr.*
Controls			
A. R.	3.7	15	3.1
F. B.	11	19	16
E. A.	4.0	12	3.7
P. McS.	8.8	14	5.3
V. B.	3.1	15	1.5
MEAN	5.9		5.9
P.M.A.			
R. T.	3.4	13	16
H. L.	0.8	12	5.8
J. E.	6.0	13	3.0
W. B.	6.3	15	1.8
MEAN	4.1		6.6

* None of the means are significantly different according to the "t" test.

EFFECT OF FORTIFICATION OF BREAD ON THE NUTRITIONAL STATUS OF VARIOUS GROUPS OF INDIVIDUALS IN THE U.S.A.

If data were available on the prewar incidence of avitaminosis and malnutrition among the alcoholics of Bridewell, it would be possible to make direct comparisons on the appearance or disappearance of nutritional disorders in alcoholics during the past 12 years. Unfortunately, such data were not collected, nor are they available. It may be argued that the nutritional status of the pre-war alcoholic

in Chicago was in no way different from that which prevails at present. That is, in contrast to the prewar alcoholics of Boston, Cleveland, and New York (among whom malnutrition was not unusual), the incidence of florid deficiency disease may have been low among the prewar alcoholics of Chicago. If this situation existed at that time, it would mean that the diet or environment of the prewar alcoholic of Chicago was unusually different from the diet and environment of the alcoholic living in large cities in the rest of the United States. This we do not believe. In fact, it is the opinion of two of the authors (F. S. and R. M. K.—both of whom had considerable experience in the study of alcoholics in Boston from 1938 to 1947) that, at present, the types and quantities of food consumed by the Chicago alcoholic do not differ grossly from those eaten by his prewar colleague in Boston. Moreover, both groups lived in similar squalid surroundings and were subject to similar environmental trauma and exposure. To R. M. K. and F. S., the patients admitted to the alcoholic ward of the Boston City Hospital and the alcoholics presently admitted to the Bridewell seem to be cast from the same mold.

Incidence of Alcoholic Pellagra

The above observations and speculations strongly suggest that 12 years ago florid deficiency syndromes would have been observed more commonly among the Bridewell alcoholics than at present. Studies have been made (from hospital records and charts) of the incidence of malnutrition and various deficiency states among alcoholic and nonalcoholic persons admitted to the Boston City and Cook County Hospitals from 1938 to 1945, and the data bear out this point.

At the Boston City Hospital between 1938 and 1945, 5.5 to 7.5 per cent of all admissions were alcoholics. At Cook County Hospital exact figures for total admissions were difficult to obtain but the incidence of primary and secondary diagnoses of "alcoholism" on the wards was steady from 1939 to 1945. At both the Boston City Hospital and at Cook County Hospital diagnoses of "avitaminosis" among alcoholics were much less in 1944 than in 1939. However, as perusal of a number of charts of patients diagnosed as having "avitaminosis" did not usually give satisfactory evidence for the clinical diagnosis, these figures are not worth presenting. Since florid pellagra is the one deficiency syndrome which is usually not difficult to diagnose, only data on pellagra will be presented at this time. All diagnoses of pellagra listed in the records of the Boston City Hospital were verified by a study of the detailed case histories drawn from the files. Unfortunately, case histories were not available at Cook County Hospital. The data from these hospitals are plotted in Table VIII and Table IX. Examination of these data

TABLE VIII

Diagnoses of Alcoholic Pellagra at Boston City Hospital and Cook County Hospital (1938–45) Compared with U. S. Production of Synthetic Vitamins During Same Period of Time

Year	Alcoholic pellagra: Total number of cases		U. S. production of synthetic vitamins in thousands of pounds		
	B.C.H.*	C.C.H.†	Niacin	Riboflavin	Thiamine
1938	19	‡	...	0	0
1939	16	12	...	0	0
1940	17	15	3.8	0	0
1941	14	13	143.0	3	0
1942	6	1	200.0	16	0
1943	6	1	163.0	72	0
1944	5	0	939.0	4	84
1945	‡	1	958.0	68	169

* Boston City Hospital, Boston, Mass.
† Cook County Hospital, Chicago, Ill.
‡ No data available.

TABLE IX

The Incidence of Pellagra and Cirrhosis Among Alcoholics (Boston City Hospital and Cook County Hospital 1938–45)

Year	Boston City Hospital		Cook County Hospital	
	Pellagra per thousand alcoholics	Cirrhosis per thousand alcoholics	Pellagra per thousand alcoholics	Cirrhosis per thousand alcoholics
1938	8.4	42.5	*	*
1939	7.0	57.2	29.9	46.5
1940	6.5	42.2	24.0	45.5
1941	5.9	41.5	20.4	54.9
1942	2.0	39.0	5.8	75.5
1943	2.0	39.9	2.1	50.9
1944	2.6	60.1	0	43.6
1945	*	*	1.7	31.6

* No data available.

shows a sharp drop in the incidence of pellagra among alcoholics in the year 1942 and indicates that the incidence of admissions for alcoholism and for cirrhosis with alcoholism did not change materially between 1938 and 1945. Moreover, it can be seen that the sharp fall in incidence of pellagra in 1942 coincides with the sudden upsurge in manufacture and sale of synthetic niacin and riboflavin, which were used, in the main, to fortify cereals.

Bean *et al.*[64] also found a sharp drop in the incidence of pellagra in Cincinnati in 1941. Our interest in nutritional syndromes is known to many of the medical residents of Cook County Hospital, and since 1947 we have been called in consultation to see many patients suspected of having florid nutritional disease. In all these years we have seen only two cases of frank pellagra in alcoholics. One patient had a benign stricture of the esophagus, the other had a neoplasm of the stomach. On the other hand, cases of scurvy and alcoholism are not uncommon, and perusal of the records of Cook County Hospital shows that admission rates for alcoholism and scurvy have not changed much since 1938, when synthetic ascorbic acid was first produced in quantity.

Florid Primary Pellagra in Nonalcoholic Individuals

As far as we are aware, there are no data available which relate improved nutritional status of groups of nonalcoholic individuals to fortification of cereals. There has been a steady decline in pellagra in the Southern states for some years[65] and this improvement is probably due to an improved economic situation and to the educational programs initiated by the U. S. Public Health Service. Dr. V. P. Sydenstricker of the University of Georgia[66] informed us that pellagra has virtually disappeared from the rural areas of the state and he believed that this was because the population in the country had changed their food habits. Instead of eating home-baked corn-meal breads they had switched to the purchase of fortified wheat breads baked in large factories in the city and delivered on rural routes. Mr. J. L. Nason, president of the Colonial Baking Company, Augusta, Ga., has been kind enough to give us data on the consumption of "baked goods" sold by his firm in *rural* areas of Georgia and South Carolina for the years 1940 to 1948. The consumption for 1940–42 was 8.7 million pounds; for 1943–45 it increased to 13.7 million pounds and for 1946–48 it rose to 17.1 million pounds.[67] Since the rural population in Georgia did not increase by more than 10 per cent from 1940 to 1948,[68] and as the consumption of breads has doubled, it is obvious that the change in incidence of pellagra in rural districts of Georgia may be related, in part, to the fortification of cereals and cereal products.

Recapitulation

Phipard and Stiebeling[56] have shown that the per capita consumption of "protective foods" has increased during the past decade and that an increasing amount of money is being spent on food. Although the general nutritional status may have improved, these authors point out that there are still many individuals who do not have sufficient funds to buy adequate amounts of "protective foods" when judged according to the recommended allowances of the Food and Nutrition Board.[54] Therefore, they conclude, malnutrition must still be common. Now, it certainly seems reasonable to assume that the alcoholic, such as we studied, eats the worst diet of the population—excepting, of course, the infrequent food-faddist, the solitary widower, and patients who have conditioned malnutrition. In the previous decade these alcoholics suffered from vitamin deficiency diseases. At present the incidence of such diseases among alcoholics is very low. Our data indicate that although malnutrition (as shown by underweight) occurred in about 30 per cent of the Bridewell alcoholics, florid avitaminosis was most uncommon. If the population group that consumes the worst diet shows little evidence of avitaminosis, then other population groups whose intake of "protective foods" is better probably are not malnourished with respect to B-complex vitamins. This being the case, Phipard and Stiebeling's[56] conclusions cannot be accepted. Furthermore, many such as Culver[70] agree that use of the recommended

allowances of the Food and Nutrition Board[54] as a yardstick for assessing malnutrition is indeed misleading. The published values of the Board are *not* minimal requirements but rather they are *recommended* allowances. For example, the recommended allowance of the Food and Nutrition Board for niacin in sedentary males is 12 mg. per day. Horwitt[69] has a group of 16 men living on diets containing less than 6 mg. niacin and less than 300 mg. tryptophan per day. Although the men have been eating these diets exclusively for nearly two years, not a single man has developed pellagra.

We conclude that among the factors that may be contributing to the surprising lack of avitaminosis among chronic alcoholics, the most significant factor is fortification of bread and cereals. Actually this is the only factor that has changed in the past 12 years in so far as the food used by the alcoholic is concerned. Concurrently with the enrichment program, the incidence of florid nutritional deficiency disease (except "underweight") among alcoholics dropped almost to the vanishing point.

On the basis of these arguments we take the position that primary avitaminosis is uncommon among the population of the United States. That is, avitaminosis due to inadequate intake of nutrients is uncommon. Among three groups, however, avitaminoses are still frequently observed. They are seen in those suffering from conditioned malnutrition, in those who are food-faddists, and in those solitary individuals, like the aged widower and the infant, who know not what they do.

Summary

Approximately 16,000 inmates of the House of Correction of the City of Chicago (56 per cent of whom were alcoholics) were screened in 1948–49 for classical nutritional deficiency syndromes; 451 newly admitted alcoholics were given careful nutritional examinations during the "pellagra season," and detailed, serial, physiological, and biochemical observations were made on 24 selected alcoholics before and during therapy.

Among the 451 newly admitted inmates 23 per cent were grossly underweight. Their average hemoglobin was 15.2 Gm./100 ml. Among the 24 selected alcoholics, 39 per cent were grossly underweight. Their average hemoglobin and total protein was 12.3 Gm./100 ml. and 6.87 Gm./100 ml., respectively. The admission fasting hour excretion of thiamine and riboflavin by these selected men ranged from 0.7 to 20 and 1.7 to 164 μg./hr., respectively. These levels of excretion of thiamine and riboflavin agreed closely with those reported for active healthy young men.

Among all these men were found only 2 with pellagra, 1 with possible beriberi, 3 with florid ariboflavinosis, 1 with Wernicke's encephalopathy, and 7 with possible nutritional polyneuropathy. No cases of shipboard scurvy, xerophthalmia, or gross phrynoderma were detected. In all, 2.2 per cent of the men were judged to have clinical evidence of avitaminosis.

To explain this unexpectedly low postwar incidence of avitaminosis among a population notoriously subject to nutritional disturbances, pre- and postwar comparisons were made of the incidence of deficiency states among alcoholics in Chicago's Cook County Hospital and the Boston City Hospital. Data from various agencies were analyzed and field observations were made in the "Skid Row" area of Chicago. The end results indicated no significant changes in eating habits, economic status, or alcoholic consumption of the Chicago alcoholic. Vitamin pills and nutrition education have passed him by. The science of fermentation and distillation of spiritous liquors is traditional and liquors are not fortified with vitamins.

The only innovation since 1938 which bears on the alcoholic's nutritional status has been vitamin enrichment of bread, started in Chicago in 1940–41. Alcoholic pellagra virtually disappeared from Cook County Hospital in 1942–43 when niacin, for flour enrichment, was first made by the ton. The alcoholic eats mainly fortified bread, and we conclude that this food habit has been the most significant factor contributing to the present surprising lack of avitaminosis among alcoholics. On the basis of observations on the alcoholic's

nutriture, we take the position that primary avitaminoses are uncommon among the population of the United States.

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Resumen

La ausencia de avitaminosis en alcoholistas

Alrededor de 16.000 presos de la Casa Correccional de Chicago (de los cuales el 56% eran alcoholistas) fueron examinados durante los años 1948–49 para determinar la existencia de síndromes clásicos de deficiencias nutritivas. 451 alcoholistas recientemente admitidos fueron sometidos a cuidadosos exámenes nutritivos durante la "estación pelagrosa" y en 24 alcoholistas seleccionados se realizaron determinaciones fisiológicas y bioquímicas detalladas y repetidas antes del tratamiento y durante el mismo. De estos 451, el 23% mostraban una grosera deficiencia en su peso y su promedio de hemoglobina fué de 15,2 gr. por 100. De los 24 alcoholistas seleccionados el peso del 39% estaba groseramente disminuido y los promedios de hemoglobina y proteina total sanguínea fueron de 12,3 gr. por 100 ml. y 6,87 gr. por 100 ml. respectivamente. La excreción por hora de tiamina y riboflavina al ser admitidos y mantenidos en ayunas osciló entre 0,7 a 20 y 1,7 a 164 mg. respectivamente. Estos niveles excretorios de tiamina y riboflavina fueron muy similares a los encontrados en hombres jóvenes, sanos y activos.

Entre todos estos individuos se encontraron solamente 2 casos de pelagra, 1 de posible beri-beri, 3 de arriboflavinosis florida, 1 de encefalopatía de Wernicke y 7 de probable polineuropatía nutritiva. No se encontraron casos de escorbuto, de xeroftalmia ni de frinoderma evidente. En total se consideró que el 2,2 % de estos individuos presentaban evidencias clínicas de avitaminosis.

Para explicar esta incidencia post-bélica, inesperadamente baja de avitaminosis entre un grupo notóriamente sujeto a trastornos nutritivos, se realizaron estudios comparativos de la incidencia de estados carenciales antes y después de la guerra en alcoholistas del Cook County Hospital de Chicago y del Boston City Hospital. Se analizaron los datos obtenidos por diversas agencias y se realizaron observaciones directas en los barrios bajos de Chicago. Los resultados finales no demostraron cambios significativos en los hábitos alimenticios, en el estado económico o en el consumo de alcohol del alcoholista de Chicago. Los preparados vitamínicos y la educación nutritiva no les habían afectado en absoluto. Los métodos de fermentación y destilación de los licores espirituosos son los tradicionales y las bebidas alcohólicas no llevan agregados vitamínicos.

La única innovación desde 1938 que afecta el estado nutritivo del alcoholista ha sido el enriquecimiento vitamínico del pan iniciado en Chicago en 1940–41. La pelagra alcohólica desapareció virtualmente del Cook County Hospital en 1942–43, cuando la niacina, para el enriquecimiento de las harinas, comenzó a prepararse por toneladas. El alcoholista come principalmente pan enriquecido, lo que nos permite concluir que esta costumbre alimenticia ha sido el factor más significativo que ha contribuido a la sorprendente ausencia de avitaminosis en los alcoholistas, observada en la actualidad. Basándonos en las observaciones de la nutrición de los alcoholistas, consideramos que las avitaminosis primarias son raras en la población de los Estados Unidos.

PYRIDOXINE DEFICIENCY *in the* HUMAN INFANT

By SELMA E. SNYDERMAN, M.D., L. EMMETT HOLT, JR., M.D., ROSARIO CARRETERO, M.D.,* AND KATHRYN JACOBS, M.D.

ALTHOUGH THE EXISTENCE of pyridoxine has been known since 1934 when György described a B factor that was curative for rat dermatitis,[1,2] very little is known about man's requirement for it, and a specific human deficiency syndrome has not been described.

The removal of pyridoxine from the diet of various experimental animals results in a set of rather well-defined symptoms which include dermatitis, neurologic manifestations, and anemia. Skin lesions consisting of a weeping scaly dermatitis with localized edema have been reported in rats,[3] mice,[4] and monkeys,[5] but are said not to occur in chicks.[6] Severe convulsions occur in chicks,[6] swine,[7] calves,[8] and ducks;[9] in addition, deficient mice have suffered from an ataxic gait,[4] and ducks have had difficulty in standing and paralysis of their legs. A hypochromic, microcytic anemia follows pyridoxine deprivation in guinea pigs,[10] dogs,[11] swine,[12] and monkeys.[13] An associated leukopenia due to a decrease in the number of lymphocytes occurred in the monkeys studied by McCall *et al.*[13] and by Rinehart and Greenberg;[14] there was no change in the white blood cell series of the monkeys reported by Poppen *et al.*[5] nor of the swine followed by Cartwright *et al.*[12]

A few other less commonly occurring sequelae of pyridoxine restriction in animals have also been recorded. In monkeys without pyridoxine for sixteen months Rinehart and Greenberg[14] found extensive arterial lesions which closely resembled the lesions of human arteriosclerosis. Stebbins[15] demonstrated a reduced diuretic response to ingested water with a lowered resistance to water intoxication in deficient rats. A striking impairment of antibody response to sheep erythrocytes was shown to occur in deficient rats by Stoerk *et al.*,[16] and a similar reduction of response to human erythrocytes was studied by Axelrod.[17] Bowles *et al.*[18] observed vascularization, thickening, and opacity of the cornea in pyridoxine deficient rats.

From the standpoint of greater accuracy, pyridoxine should be referred to as the B_6 group of vitamins, since there are two other naturally occurring forms. These include pyridoxal—the aldehyde form, and pyridoxamine—the amine form. All three occur in such substances as yeast, liver, and rice, although the proportions of the three in each substance vary widely. It appears that the pyridoxal form is the most active in body metabolism, but there is some evidence that pyridoxamine may also function in some transamination reactions. Rabinowitz and Snell[19] concluded as a result of a study of the urinary excretions of normal adults after test doses of all three forms, that pyridoxine can be converted to the -al and -amine forms, but that these two forms cannot be converted into pyridoxine. 4-Pyridoxic acid is quantitatively

From the Department of Pediatrics, New York University College of Medicine.

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* Mead Johnson fellow in pediatrics.

the most important urinary excretion product of the B_6 complex and is highest after pyridoxal ingestion; pyridoxine, pyridoxal, and pyridoxamine are also found in the urine after ingestion of each of these forms.

Much has been learned of the biochemical functions of vitamin B_6, but just how a disturbance of these functions produces the specific symptoms seen in deficient animals is not clear. Vitamin B_6 is intimately concerned in amino acid metabolism and is essential for the complete metabolism of tryptophan. This was first suggested in 1942 when Lepkovsky and Nielsen[20] found a green pigment after treating the urine of deficient rats with iron ammonium sulfate; this compound was later identified as xanthurenic acid,[21] an intermediate metabolic product in the conversion of tryptophan to nicotinic acid. Pyridoxal phosphate is also necessary for the synthesis of tryptophan from indole and serine by cell free enzyme preparations derived from neurospora.[22] Pyridoxal has a codecarboxylase function, that is, it acts as a coenzyme for the enzyme that removes the carboxyl group from amino acids with the resulting formation of an amine and the liberation of carbon dioxide. This function has been demonstrated for the following amino acids: tyrosine,[23] lysine,[24] arginine, and glutamic acid.[25] Members of the B_6 group are also essential for activating the transamination reactions of amino acids.[26]

Vitamin B_6 is also active in many phases of fat metabolism, including its transport, oxidation, synthesis, and deposition, but there is, thus far, no information available concerning the exact biochemical nature of the relationship between B_6 and fat metabolism. It seems to be particularly concerned in the metabolism of the unsaturated fatty acids.[27]

Pyridoxine has been used therapeutically in many different conditions, but appraisal of its efficacy is rendered difficult because of the lack of controls and follow-up studies in most of the reported studies. It has been reported as effective in curing cheilosis associated with B-complex deficiencies.[28] It seems definitely not to be of value in the treatment of epilepsy,[29] Parkinsonism,[30] and progressive muscular dystrophy,[31] but some increase in a feeling of well-being did occur in the various neuritides treated by Stone.[32] The results of the therapeutic use of pyridoxine in various skin disorders have not been clear cut.[33] Although some of the earlier studies indicated a beneficial response of the nausea and vomiting of pregnancy to pyridoxine,[34,35] a carefully controlled study by Hesseltine[36] failed to substantiate the earlier findings. However, three different groups of workers[37,38,39] have reported consistently good results in the treatment of radiation sickness with pyridoxine.

An attempt to produce pyridoxine deficiency in the adult has been tried on several occasions without clearly defining its role in human nutrition. After 54 days of pyridoxine deprivation, no signs or symptoms occurred in the subject of Hawkins and Barsky's[40] study that could unequivocally be considered to be due to B_6 deficiency. Gellhorn and Jones[41] gave a low pyridoxine diet and desoxypyridoxine for 2 weeks to six cases of lymphosarcoma and leukemia without observing any signs that they considered to be due to B_6 deficiency except for two transient epileptic convulsions which responded to a reduction in the dose of desoxypyridoxine. Mueller and Vilter[42] also used desoxypyridoxine in addition to a B-complex low diet in an attempt to produce pyridoxine deficiency. They noted seborrhea-like lesions about the eyes, nose, and mouth within 2 to 3 weeks, and also cheilosis, glossitis, and stomatitis. They did not observe any neurological or hematologic manifestations of pyridoxine deficiency. It seems quite possible that the use of an antimetabolite such as desoxypyridoxine may not give a true picture of a vitamin deficiency, since it may interfere in only a small part of the vitamin's function; this has been shown to be true in the case of thiamine and its antagonists by Woolley and Merrifield.[43] Also, the intrinsic toxicity of the vitamin analogue not related to its antimetabolic capacity may confuse the picture.

The failure to metabolize tryptophan to its usual end products in the absence of pyridoxine was demonstrated in human subjects by Greenberg *et al.*[44] These workers found that the administration of 10 Gm. of dl-tryptophan resulted in a much larger urinary excretion of

xanthurenic acid after pyridoxine had been omitted from the diet for 2 to 3 weeks than during the control periods on normal diets. One other study concerned with pyridoxine in the human subject is that of McGarrity[45] and his group, who found that pyridoxine was capable of raising the low blood urea nitrogen of women with hyperemesis gravidarum to the level normally found during pregnancy; it had no effect on the normal blood urea nitrogen of pregnant or non-pregnant women.

The recent report by Hunt and McCrory[46] of severe, prolonged convulsions in an infant which were controlled only by the administration of pyridoxine provokes us to report, at this time, a study of pyridoxine deprivation in the human infant which we carried out in the winter of 1948–49. This study was designed to determine if pyridoxine were indeed required by the human and what the signs and symptoms of such a dietary restriction would be in the growing infant. We felt justified in using infants as subjects for such a study for the following reason. Our subjects were severely mentally defective infants. Such infants, boarding on acute infants' wards, run greater risks from contracting various contagious illnesses than from a carefully controlled nutritional deficiency carried out on an isolated ward while receiving very specialized nursing and medical care. The following report describes our findings in two infants who were maintained on pyridoxine-free diets.

Experimental

The subjects were two male infants, M. L. and G. E., aged two and eight months, who weighed 5.1 and 3.9 Kg., respectively, at the onset of the study. Each had severe cerebral defects, hydrocephalus in the one and a combination of microcephalus and porencephalus in the other. They were placed on metabolism frames for a five-day period of each week, during which time twenty-four hour urine specimens were collected.

The diet consisted of vitamin-free casein (Labco®), vitamin-free dextrimaltose,* hydrogenated cotton-seed oil† and a salt mixture (Table I). These components were mixed to give the following distribution of calories: protein 15 per cent, carbohydrate 50 per cent, and fat 35 per cent. Each infant was given 100 calories per kilogram of body weight daily. All vitamins were supplied as supplements: vitamins A and D as oleum percomorphum,‡ 15 drops daily, and the water-soluble vitamins as a synthetic mixture (Table II).

TABLE I
Composition of the Salt Mixture

	%
NaCl	18.9
CaH_2PO_4 (anhydrous)	25.0
$MgSO_4$ (anhydrous)	6.8
$KHCO_3$	44.4
KCl	2.88
Fe_3 Citrate	2.21
$CuSO_4$ (anhydrous)	0.24
$MnSO_4$ (anhydrous)	0.15
KI	0.015
NaF	0.03

TABLE II
Composition of the Vitamin Mixture

	Mg.
Thiamine	0.38
Riboflavin	2.0
Nicotinamide	0.85
Pyridoxine hydrochloride	0.67
Calcium pantothenate	3.5
Para-amino benzoic acid	0.5
Choline chloride	147.0
Inositol	180.0
Ascorbic acid	25.0
Folic acid	0.05
Biotin	0.03

The twenty-four hour urine specimens were preserved by the addition of 3.5 cc. of 6 *N* HCl and a layer of toluene was added. The urines were pooled to form one three-day and one two-day specimen for each week. Pyridoxic acid determinations were performed on the three-day samples, while pyridoxine hydrochloride assays were made on both specimens.

Urinary pyridoxic acid determinations were performed fluorometrically by the method of Huff and Perlzweig.[47] The pyridoxine hydrochloride content of the urine was assayed

* Specially prepared by Mead Johnson and Company through the courtesy of Dr. Warren M. Cox, Jr.
† Crisco. Contributed by Procter and Gamble.
‡ Contributed by Mead Johnson and Company.

microbiologically* by the method of Atkin, Schultz, Williams, and Frey.[48] The method of Huff and Perlzweig[49] was used to determine the amount of urinary N^1-methylnicotinamide. Hemoglobin levels were obtained by the use of a photoelectric colorimeter. The method of Wintrobe[50] was employed to determine the hematocrit values.

Throughout the period of study, these subjects received very careful medical and nursing supervision. Physical examinations were performed daily and daily weights were recorded. Roentgenograms of the lungs and long bones were taken monthly. There were frequent routine urinalyses, blood NPN, protein, Na, K and Cl determinations, electrocardiograms and ophthalmologic examinations. Red and white blood counts, hemoglobin and hematocrit determinations were carried out weekly except at the more critical points in the study when they were performed daily. The ability of these infants to convert tryptophan to N^1-methylnicotinamide was tested at irregular intervals by the intravenous administration of 1 Gm. of *l*-tryptophan; the details of this test have been reported elsewhere.[51]

The procedure consisted of a control period when the standard vitamin mixture providing a daily intake of 0.67 mg. of pyridoxine HCl was given and baseline values for all the laboratory data were obtained. This was then followed by the complete removal of pyridoxine from the vitamin mixture.

Results

These two subjects showed certain similarities and dissimilarities in response to long-term deprivation of pyridoxine. The similarities will be discussed first.

The withdrawal of pyridoxine from the diet resulted in a prompt fall in both pyridoxine HCl and 4-pyridoxic acid urinary excretion in subject G. E.; the same changes, somewhat delayed, took place in the urinary output values of the other subject also. Urinary 4-pyridoxic acid levels fell to zero, whereas the pyridoxine HCl values, although quite low, occurred always in a measurable range —0.2 to 2 μg. daily. In both subjects the fall in 4-pyridoxic acid excretion took place first.

Both subjects had a similar response in their ability to convert tryptophan to N^1-methylnicotinamide. During the control period, the intravenous administration of 1 Gm. of *l*-tryptophan resulted in an N^1-methylnicotinamide output which was at least 2 to 3 times greater than that which occurred when no additional tryptophan was supplied. This conversion no longer took place after the subjects had been on the pyridoxine deficient diet for 60 days. Since this ability to convert tryptophan to N^1-methylnicotinamide was first tested on the 60th day, it is quite possible that this biochemical defect occurred much sooner; indeed, a subsequent study on one subject in whom this test was carried out at much more frequent intervals showed that this defect appeared on approximately the 20th day of deprivation.

Both subjects failed to gain weight as a result of pyridoxine deficiency—subject M. L. after 33 days and subject G. E. after 73 days.

Their further courses illustrated two different symptom complexes through which pyridoxine deficiency may become clinically evident. These consisted of convulsions in M. L. and anemia in G. E.

On the 76th day of deprivation, subject M. L. suffered a series of severe convulsions. These followed a period of 4 days during which he had seemed more listless than usual and his appetite was impaired. The seizures, clonic and tonic in character, were preceded by a shrill cry and were accompanied by cyanosis. They continued for two hours and were succeeded by a coma during which there were occasional twitches of the extremities. During the comatose state, respirations were dysrhythmic, the pulse was rapid (180) and the infant did not respond to painful stimuli. Tendon reflexes were present, but the pupils were constricted and did not react to light. Aside from oxygen during the seizure, no other therapy was given until he received 50 mg.

* The assays of pyridoxine hydrochloride and pyridoxic acid were carried out in the Food Research Laboratories, Long Island City, under the direction of Dr. B. L. Oser.

of pyridoxine hydrochloride intravenously. Within three hours he started to show signs of improvement, consisting of slight reaction to painful stimuli, sluggish pupillary responses to light, and the reappearance of sucking movements. By the next morning, he was fully recovered and seemed his usual self. Although convulsions are known to occur frequently in defective children, we believe that this particular episode was brought on by pyridoxine deprivation, because this symptom had not occurred before nor since this one occasion. An electroencephalogram taken 1 week later did not reveal any asymmetry in the wave pattern or any abnormal discharges. The administration of this one dose of pyridoxine had a striking effect on the weight curve, resulting in the gain of 0.8 Kg. in the ensuing 10-day period. No further attempt was made in this subject to produce more symptoms of pyridoxine deficiency.

Subject G. E. began to have a fall in his hemoglobin values at approximately the 30th day of deprivation which plateaued out around the 50th day. The administration of ferrous sulfate from the 60th day on was without effect. The red blood count and hematocrit levels were maintained until the 110th day of the deficiency regime when a gradual diminution of these values began. Beginning at the 130th day, there was an abrupt change in the hemogram. Within 10 days, the red blood count had fallen to 2.5 million, the hemoglobin to 5.5 Gm., and the hematocrit to 16 per cent. This anemia was microcytic and hypochromic, with a mean corpuscular volume of 64 cubic microns, a mean corpuscular hemoglobin of 22 micromicrograms, and a mean corpuscular hemoglobin concentration of 34 per cent. There were no evidences of excess hemolysis and the cell fragility was normal. There were no accompanying alterations in the white cell series, both the total white blood cell count and the myeloid-lymphocytic ratio remaining unchanged. Examination of the bone marrow at this time revealed a normoblastic hyperplasia.* The administration of 50 mg. of pyridoxine hydrochloride intravenously, followed in 4 days by a daily oral maintenance dose of 1 mg., brought about a striking hematologic remission. The reticulocyte count, previously within normal limits, started to rise within 72 hours and reached a peak of 12 per cent on the 4th day. A definite rise in both hemoglobin and red blood cell figures was noted within 1 week and they approached control levels in 24 days. A rapid gain in weight also took place.

In this subject, it was possible to follow the tryptophan-N^1-methylnicotinamide conversion after supplementation with pyridoxine was started. In marked contrast to the clinical remission, there was a delay of 7 weeks before the conversion could be demonstrated for the first time.

An attempt was made, after we felt that this infant was saturated with pyridoxine, gradually to decrease the daily intake in an effort to find a point which no longer produced a large urinary spill of 4-pyridoxic acid and pyridoxine. This part of the study was not

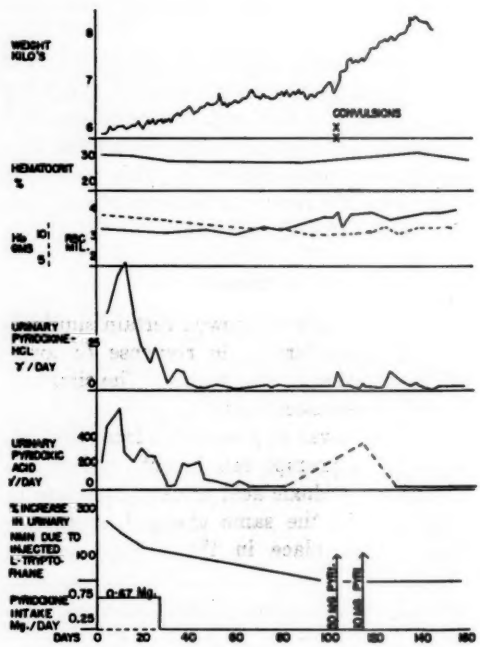

Fig. 1. Effect of pyridoxine restriction: Subject M. L.

* We are indebted to Dr. Edward H. Reisner, Jr., for this report.

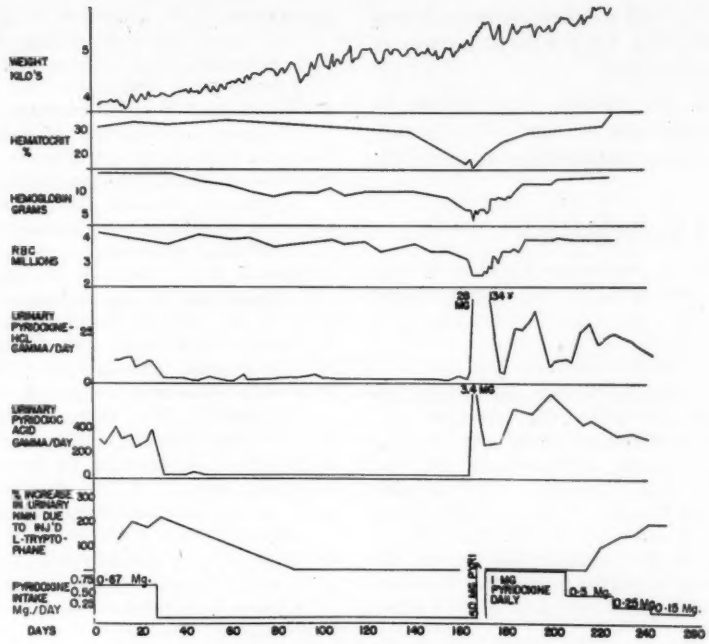

Fig. 2. Effect of pyridoxine restriction: Subject G. E.

completed, since it was interrupted after the intake had been decreased stepwise to 0.15 mg. of pyridoxine daily. At this low intake there was still a considerable urinary excretion of 4-pyridoxic acid and pyridoxine, indicating that this intake was above the requirement for this infant.

Detailed protocols for the two subjects are given graphically in Figures 1 and 2.

Discussion

Although our experience thus far with pyridoxine deficiency is limited to two subjects, it is apparent that this vitamin plays an important role in human nutrition. It is necessary for growth, for red blood cell formation, and for the maintenance of the well-being of the central nervous system.

These studies suggest that the ability to convert tryptophan to N^1-methylnicotinamide may be used as a test of pyridoxine deficiency in the human. Its disappearance on the 20th day of deprivation long before symptoms were apparent, and the lag in its return to normal after the institution of therapy, despite clinical remission, suggest that greater tissue stores of pyridoxine are necessary to allow this reaction to take place than to prevent the other evidences of deficiency. Hence, it may prove of value in detecting subclinical pyridoxine deficiency states in the human.

Our studies do not define the infant requirement for pyridoxine. It may well be under 0.15 mg. per day for an infant maintained under the conditions of this study. In this connection, it is interesting to note the pyridoxine content of cow's and human breast milk. The former has been reported to contain a mean of 0.51 to 0.66[52,53] mg. per liter, while the latter contains a mean of 0.04[54] and 0.18[55] mg. per liter according to the only two studies available.

Summary

Pyridoxine deprivation in two human infants resulted in an arrest of weight gain and failure of the ability to convert tryptophan to N^1-methylnicotinamide in both. In one subject, it resulted in convulsive seizures; in the other it provoked a severe microcytic hypo-

chromic anemia. All of these symptoms and signs were corrected by the introduction of pyridoxine into the diet.

The ability to convert tryptophan to N^1-methylnicotinamide is suggested as a biochemical test for pyridoxine deficiency in the human.

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We should like to express our gratitude to Miss Eileen Hasselmeyer, R.N., for the supervision of these patients.

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Resumen

Deficiencia de piridoxina en el niño pequeño

En 2 niños la supresión de piridoxina produjo una detención en el aumento de peso y una incapacidad para transformar el triptofano en N^1-metilnicotinamida. En uno de ellos dió origen a ataques convulsivos, y en el otro provocó una anemia microcítica-hipocrómica severa. Todos estos síntomas y signos se corrigieron por la introducción de piridoxina en la dieta.

La capacidad para transformar el triptofano en la N^1-metilnicotinamida se sugiere como un test bioquímico para investigar la deficiencia de piridoxina en el hombre.

Arteriovenous Glucose Differences, METABOLIC HYPOGLYCEMIA AND FOOD INTAKE *in Man*

By THEODORE B. VAN ITALLIE, M.D.,* RACHEL BEAUDOIN, D.SC.† AND J. MAYER, PH.D., D.SC.

PREVIOUSLY REPORTED studies on animals[1,2] have shown that experimentally induced alterations in level of blood glucose significantly modify food intake. These results provided a basis for formulation of the "glucostatic" theory of food intake regulation.[2] Briefly, this theory postulates that, in the normal animal, variations in the blood glucose level exert a regulatory influence on food intake. Other experiments[3] have indicated that a hypothalamic center may mediate between blood glucose levels and food intake.

In order to extend the glucostatic theory to include conditions associated with abnormal levels of blood sugar, such as diabetes mellitus, the concept of "effective" blood sugar levels has been proposed,[4] and has been applied to alloxan diabetes in the rat,[4] and the hereditary obesity-diabetes syndrome in the mouse.[5]

"Effectiveness" of blood glucose denotes its ability to enter into cells. Arteriovenous glucose differences largely measure removal of glucose by tissues[6,7] and, accordingly, may be regarded as an index of the effectiveness of blood glucose. For example, in uncontrolled diabetes mellitus, arteriovenous glucose differences are frequently negligible (*vide infra*) and thus hyperglycemia and "metabolic hypoglycemia" may be said to coexist. Since arteriovenous glucose differences may provide information concerning tissue removal of blood sugar at a given arterial level, such differences, according to the glucostatic theory, should enhance correlation of arterial glucose levels with food intake, and feelings of "hunger" or "satiety."

It is acknowledged at the outset that feelings involving desire for food are not in any sense quantifiable.[8] Yet they represent a conscious expression of one of the most precise regulatory devices in biology—the mechanism which regulates energy balance. Moreover, any theory which attempts to explain food intake regulation and which cannot account for feelings of hunger is necessarily inadequate. Thus, a correlation, however imprecise, between feelings of hunger, or absence of such feelings, and values which are indices of carbohydrate utilization is justifiable as a first approximation.

Regardless of the complex homeostatic forces which condition glucose uptake by cells, shrinkage of the peripheral arteriovenous glucose difference in the normal subject ordinarily represents a response to carbohydrate depletion.[9] Since hunger similarly has been postulated to be a response to "metabolic hypoglycemia," a correlation in time between the two might be anticipated.

The present experiments on adult human

From the Department of Nutrition, Harvard University School of Public Health, and the Medical and Surgical Clinics, Peter Bent Brigham Hospital, Boston, Mass.

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* Present address: St. Luke's Hospital, New York, N. Y.

† Present address: Institut de Diététique et de Nutrition, Université de Montréal, P. Q., Canada.

subjects were designed to determine to what extent the glucostatic theory can account for the desire for food and absence of such desire. Therefore, an attempt has been made (a) to relate capillary (arterial[10]) glucose values and arteriovenous glucose differences in time, to state of nutrition under strictly controlled or known conditions of dietary intake; and (b) to relate feelings of hunger or lack of such such feelings to variations in capillary glucose levels and the associated arteriovenous glucose differences under various experimental conditions.

Uptake of glucose by the brain as a whole appears to be insensitive to hormonal influence.[11] However, the pragmatic assumption has had to be made that variations of the "Δ-glucose" (which, in this instance, represents the difference between the glucose content of finger tip [arterial] blood and antecubital venous blood) are ordinarily indices of glucose assimilation by cells elsewhere in the body, including specialized "glucoreceptors" in the central nervous system.[3]

Procedure and Results

METHODS

Venous blood was always obtained from the antecubital area. Capillary blood was collected by direct pipetting from a finger tip after cutaneous puncture. Subjects were studied in the resting state in a comfortable warm room kept at virtually constant temperature.

The Somogyi-Nelson semi-micromethod[12,13] was used to measure glucose in whole blood. Determinations were done in duplicate on 0.2-ml. samples.

In experiments 3, 4, 5, and 6, dietary intake was carefully recorded for at least 3 days prior to the blood glucose studies. When direct analysis and weighing of diets was not done, dietary information was calculated from the tables of food composition of Bowes and Church.[14]

SUBJECTS

Six volunteer subjects were studied. Five of them were in good health; the sixth had severe diabetes mellitus of long standing. The relevant data concerning the subjects and their preparatory dietary regimens are in Tables I and II.

Virtually simultaneous capillary and venous samples were taken at frequent intervals from these subjects during the "experimental day" and variations in arteriovenous glucose differences (Δ-glucose) were related to food intake, nutritional status and feelings of hunger in 6 different experimental situations.

TABLE I
Experimental Subjects

Subject		Age	Weight	Height	Diagnosis
			Kg.	*Cm.*	
P. A.	♂	24	78.1	188	Normal
A. G.	♂	23	83.0	189	Normal
M. M.	♂	21	67.8	179	Normal
M. L.	♀	41	50.0	157.5	Diabetes mellitus
L. F.	♂	28	78.1	176.5	Normal
N. R.	♀	33	67.7	173.0	Normal

Since the essential conclusions can be derived from four of the experiments, these are described in detail. Results of the other two experiments are given in Table IV.

EXPERIMENTS

1. Constant Adequate Dietary Intake:

Plan. Subject P. A. was studied in the hospital for 20 days and was given a constant weighed diet of known composition. Intake of calories and nitrogen was adequate for maintenance of body weight and nitrogen equilibrium. Metabolic studies* with respect to nitrogen, potassium, and sodium balances were carried out.

Blood glucose studies were performed on the fifth and twentieth days of the experimental study.

Results. During the 20-day period of study, P. A. lost only 0.8 Kg. During the 4 days preceding the first glucose study, P. A.'s weight decreased by 0.1 Kg. He did not complain of hunger at any time during the experimental period and felt well during his entire hospital stay.

Fluctuations in capillary and venous blood glucose as determined on the fifth experimental day are shown in Figure 1. The postabsorptive Δ-glucose is 7 mg. per cent and is the smallest Δ-glucose value observed during the approximately 6 hours of observation. Relatively

*The details of these studies are omitted for economy of space, and the results stated when relevant.

TABLE II
Distribution of Constituents of Preparatory Diets

Experiment	Subject	Calories/day	Preparatory diets Carbohydrate	Protein	Fat
			Gm./day	*Gm./day*	*Gm./day*
1. Constant adequate dietary intake*	P. A.	2426	271	101	106
2. Constant inadequate dietary intake*	A. G.	1024	149	50	22
	M. M.	980	150	50	20
3. Uncontrolled diabetes mellitus†	M. L.	2000	300	70	60
4. Cortisone experiment					
(a) Control day†	M. M.	3233	248	149	191
(b) Cortisone administration†	M. M.	4154	417	158	212
5. Prolonged low fat calorically adequate intake†	L. F.	2381	445	115	7
6. Epinephrine experiment†					
(a) Control day	N. R.	2597	262	96	119
(b) Epinephrine administration	N. R.	2289	261	65	102

* Weighed intake
† Recorded intake (average for 3 days).

high values for Δ-glucose are observed during the course of the experiment, including the period immediately preceding the noon meal.

Variations in capillary and venous blood glucose were studied again on the twentieth day of the constant intake. At this time, P. A.'s activity had increased appreciably, since he was now attending classes, although he took his meals and slept at the hospital. The glucose data are shown in Table III.

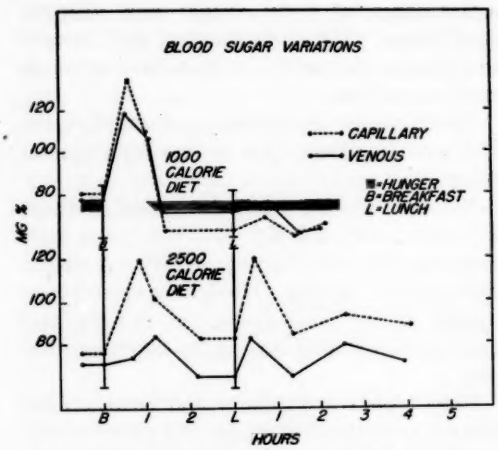

Fig. 1. Blood glucose variations in two normal subjects (A. G. ["1000 calorie diet"] and P. A. ["2500 calorie diet"]) on different constant dietary intakes. (Distribution of meal constituents for P. A. is the same as in Table III. For A. G., Breakfast: Cal. 409, C·H_2O 74.8 Gm., Pro. 7.6 Gm., Fat 6.5 Gm.; Lunch: Cal. 442, C·H_2O 49 Gm., Pro. 28.9 Gm., Fat 14.5 Gm.)

Except for the somewhat higher peaks for capillary and venous glucose after breakfast, the Δ-glucose pattern is very similar to that observed on the fifth day. No hunger sensations were reported at any time by P. A. during the seven-hour sampling period.

2. Constant Inadequate Dietary Intake:

Plan. Subjects A. G. and M. M. were studied in the hospital for 5 days. Both received constant weighed diets which were inadequate with respect to calories, and low in protein. These intakes caused weight loss, and constantly negative nitrogen and potassium balances, as disclosed by metabolic balance studies.

Blood glucose determinations were done on M. M. prior to dietary curtailment and on the fifth day after the restricted diet had been started. Glucose studies were done on A. G. on the fifth day of dietary restriction.

Results. During the 4-day period preceding the test day, A. G.'s weight decreased 2.3 Kg. He did not feel continuously hungry but epigastric "hunger" occurred much sooner after meals than ordinarily, coming on one-half to one hour after breakfast, and approximately one hour after lunch and supper. After the first acute pangs the sensation tended to subside to some extent. Following several days of dietary restriction, the subject became increasingly irritable and displayed easy fatigability.

TABLE III

Capillary and Venous Blood Glucose Values in Relation to Meals and Urge for Food

Subj. and exp.	Time after meal	Capillary glucose	Venous glucose	Δ-Glucose	Desire for food
	Min.	*Mg. %*	*Mg. %*	*Mg. %*	
P. A.	Fasting	...	85	...	
Exp. 1	Breakfast: Cal. 757, CH_2O 108 Gm., Pro. 23 Gm., Fat 24 Gm.				
	10	125	115	10	
	45	118	111	7	
	80	...	99	...	
	140	91	79	12	
	190	84	65	19	
	Lunch: Cal. 696, CH_2O 68 Gm., Pro. 40 Gm., Fat 31 Gm.				
	35	94	75	19	
	65	89	75	14	
	110	86	65	21	
	180	89	79	10	
M. M.	Fasting	82	84	−2	++++
Exp. 2	Breakfast: Cal. 345, CH_2O 57 Gm., Pro. 7 Gm., Fat 10 Gm.				
	32	168	149	19	
	66	129	112	17	
	124	93	85	8	+++
	Lunch: Cal. 259, CH_2O 43 Gm., Pro. 15 Gm., Fat 2 Gm.				
	35	163	149	14	
	65	108	94	14	
	135	75	68	7	
	260	77	75	2	++++
M. L.	Fasting	203	194	9	+++
Exp. 3	Breakfast: Cal. 319, CH_2O 35 Gm., Pro. 12 Gm., Fat 16 Gm.				
	40	322	322	0	
	68	336	343	−7	
	100	353	353	0	++
	Lunch: Cal. 367, CH_2O 60 Gm., Pro. 15 Gm., Fat 9 Gm.				
	38	544	503	41	
	102	593	581	12	
	174	556	530	26	

Variations in capillary and venous blood glucose are shown in Figure 1. The difference between the Δ-glucose variations of P. A. and A. G. throughout the day is striking. A. G.'s postabsorptive Δ-glucose is small, as in the case of P. A. Expressed as per cent increase over the fasting value, the rise in venous glucose one-half hour after breakfast is 53 per cent for A. G., compared to a 7 per cent rise exhibited during a comparable interval by P. A. The rise in venous glucose shown by A. G. is characteristic of "hunger diabetes." For A. G., Δ-glucose is 16 mg. per cent one-half hour after breakfast and it drops to 7 mg. per cent one hour after breakfast. The latter value is within the range for Δ-glucose considered normal in the fasting state. For P. A., the Δ-glucose one hour after breakfast is 33 mg. per cent and it remains between 16 and 18 mg. per cent before lunch, while that of A. G. actually reverses and becomes −8 mg. per cent.

Values for capillary glucose fall below the fasting level before lunch in the case of A. G., while the capillary glucose values of P. A. never again descend to the pre-breakfast level. For A. G. capillary and venous values rise only slightly after lunch (Fig. 1) and never actually reach postabsorptive levels. During this time A. G.'s Δ-glucose values are negative and indicate absence of any peripheral uptake of glucose.

During the 4-day depletion period preceding the glucose study, M. M.'s weight decreased 2.65 Kg. During this time he was not excessively uncomfortable, but he was constantly preoccupied with thoughts of food. His ability to concentrate while studying diminished noticeably.

Variations in blood glucose before and during the period of caloric restriction are indicated in Figure 2 and Table III respectively. Marked differences in the blood sugar response to food are observed when the 2 experimental days are compared. First, the capillary and venous curves after 4 days of dietary restriction rise to far higher levels after meals than the curves associated with a self-selected intake not preceded by previous dietary curtailment.

Second, even at hyperglycemic levels (163 mg. per cent), the Δ-glucose 35 minutes after lunch on the fifth experimental day is far smaller than the Δ-glucose which obtains at a much lower level (118 mg. per cent) under normal nutritional conditions. Two and one-half hours after lunch on the fifth day, the subject took a nap and when he awakened an hour and a half later he was ravenously hungry. The Δ-glucose at that time was 2 mg. per cent.

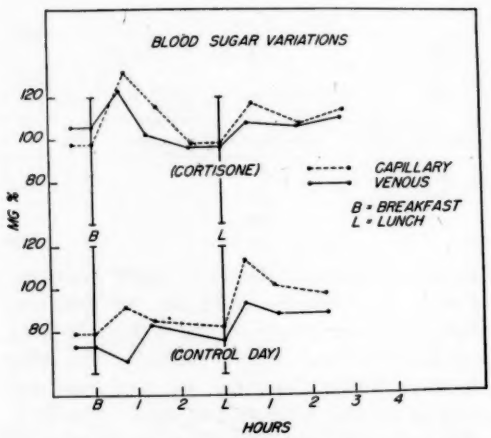

Fig. 2. Blood glucose values in a normal subject on a control day and during cortisone administration. (Breakfast: Cal. 725, C·H_2O 69.5 Gm., Pro. 24.5 Gm., Fat 40.7 Gm.; Lunch: Cal. 829, C·H_2O 108.4 Gm. Pro. 27.5 Gm., Fat 38.3 Gm.)

3. Uncontrolled Diabetes Mellitus:

Plan. Subject M. L. was studied as an outpatient. She was a severe diabetic of 20 years standing. Recently, she had been taking 5 units of regular and 40 units of protamine zinc insulin per day. For the 24-hour period prior to the glucose studies and during the experimental day she took no insulin. On the day of the test, capillary and venous glucose samples were obtained frequently from early in the morning (postabsorptive) until late in the afternoon. Her meals were self-selected.

Results. Analytic data on M. L. are shown in Table III.

Prior to breakfast, she was extremely hungry. At this time her capillary blood sugar was 203 mg. per cent and the Δ-glucose was less than 10. Following breakfast, the capillary blood sugar rose gradually from 322 to 353 mg. per cent. The Δ-glucose remained negligible, although she was not hungry until the period immediately prior to lunch. After lunch, her capillary glucose rose to 544 and then to a peak of 593 mg. per cent. At these levels Δ-glucose values were of normal magnitude. No hunger was present during the afternoon.

4. Cortisone Administration:

Plan. Because cortisone is known to increase food intake, a second study on M. M. involving oral administration of cortisone* was done. Dietary conditions of the self-selected diet taken by M. M. for control purposes in Experiment 2 were duplicated. The

* Cortisone acetate, Merck.

schedule of cortisone administration on the experimental day was as follows:

12:30 a.m. ..... 100 mg.
7:30 a.m. ..... 75 mg.
12:30 p.m. ..... 50 mg.

As in the control study, the diet 3 days prior to this experiment included an intake of calories and carbohydrate which was more than adequate to prevent impairment of carbohydrate tolerance on a dietary basis (Table II).

Results. Analytic data obtained on the control and experimental days are plotted in Figure 2. When the results for the 2 days are compared, striking differences are apparent.

The postabsorptive capillary and venous glucose values after cortisone administration are significantly higher than postabsorptive values on the control day. For example, the value for venous blood glucose before breakfast on the day of cortisone administration is 106 mg. per cent. On the control day, the value is 74 mg. per cent. Moreover, the postabsorptive Δ-glucose after cortisone is inverted.

It can be seen that following ingestion of the morning and noon meals on the day cortisone was being given, M. M.'s Δ-glucose values remain relatively small throughout, despite appreciable rises in the level of capillary glucose after meals. By contrast, the Δ-glucose values on the control day are much larger after meals, in spite of the fact that the overall level of capillary blood sugar is lower. The Δ-glucose changes observed on the control day correspond to the pattern repeatedly observed in normal subjects after ingestion of food.

On the day of cortisone administration, M. M. complained of marked hunger prior to the morning meal and felt that he was "able to eat" at an earlier time before the noon meal than on the control day. During another unrelated experiment which involved his taking appreciable amounts of cortisone, M. M.'s appetite had increased noticeably.*

5. Prolonged Low Fat, Calorically Adequate Intake:

Plan. Subject L. F. was studied during the course of his normal daily activities. For 15 days he was kept on a diet extremely low in fat but containing sufficient calories to maintain his body weight. Blood glucose studies were performed on the sixteenth day.

Results. Data for Experiment 5 are shown in Tables I, II, and IV.

6. Epinephrine Administration:

Plan. Subject N. R. was studied while she continued her daily work as a graduate student. First (Part 1), variations of capillary and Δ-glucose levels during the day in relationship to food intake and feelings of hunger were determined. Second (Part 2), similar observations were made with respect to the postabsorptive Δ-glucose before and for 4 hours following subcutaneous injection of 0.3 cc. of 1:1000 epinephrine U.S.P.

For 3 days preceding each of these tests, the diet was self-selected but very carefully recorded. Activity remained unchanged.

Results. Data for Experiment 6 are shown in Tables I, II, and IV.

Discussion

In general, a satisfactory correlation between values for Δ-glucose and desire for food could be made. When values for Δ-glucose remained appreciable (> 15 mg. per cent), hunger never was reported. A Δ-glucose approaching zero ordinarily was associated with hunger. In normal subjects, if a low Δ-glucose continued to shrink for any length of time, hunger was always reported. A negative† Δ-glucose in normal persons was invariably accompanied by hunger feelings.

Although hunger never was associated with a high value for Δ-glucose, there were exceptional situations in which low or negligible Δ-glucose values were not accompanied by hunger feelings. For example, epinephrine administration appeared to inhibit assimilation of glucose by certain tissues, yet it also sup-

* Results of a similar study on a large series of patients, confirming and extending observations on the effect of cortisone on Δ-glucose and food intake will be published soon by one of us.

† Whether small inverted arteriovenous glucose differences can exist, or whether they are due to faulty technique, is a controversial issue.[15–17]

TABLE IV
Capillary and Venous Blood Glucose Values in Relation to Meals and After Epinephrine Administration

Subj. and exp.	Time after meal	Capillary glucose	Venous glucose	Δ-Glucose	Desire for food
	Min.	*Mg. %*	*Mg. %*	*Mg. %*	
L. F.	Fasting	84	77	7	+++
Exp. 5	Breakfast: Cal. 318, CH_2O 73 Gm., Pro. 4 Gm., Fat 1 Gm.				
	35	97	88	9	
	110	74	68	6	+++
	Lunch: Cal. 865, CH_2O 102 Gm., Pro. 28 Gm., Fat 3 Gm.				
	35	93	68	25	
	125	85	67	18	
N. R.	Fasting	73	64	9	+++
Exp. 6 Part I	Breakfast: Cal. 363, CH_2O 49 Gm., Pro. 16 Gm., Fat 12 Gm.				
	40	110	64	36	
	116	83	82	1	+++
	Lunch: Cal. 627, CH_2O 71 Gm., Pro. 18 Gm., Fat 32 Gm.				
	38	134	96	38	
	121	101	88	13	
	180	81	68	13	
N. R.	Fasting	84	75	9	+++
Exp. 6 Part II	Epinephrine 0.3 ml. (1:1000 injected subcutaneously)				
	34	...	78	...	
	58	102	100	2	
	76	114	109	6	
	111	95	104	−9	
	251	73	77	−4	+++

pressed hunger (Experiment 6). It would be an oversimplification to attribute this apparently contradictory result to any one of the multifarious physiologic effects[18] of epinephrine. However, since epinephrine causes differential changes in the blood flow (and glucose assimilation) of various tissues, it is quite possible that in this experiment the antecubital Δ-glucose simply was not representative of what was going on in the "glucoreceptors."

Since M. L. (Experiment 3—Uncontrolled Diabetes Mellitus) was apparently not hungry after her breakfast at levels of blood sugar not accompanied by a measurable Δ-glucose, it must be assumed that the postulated "glucoreceptors"[3] were influenced before uptake of glucose took place in the area drained by the antecubital vein.

Unquestionably, the influence on appetite of abrupt changes in the bulk and composition of the diet, conditioned reflexes (habit), gastrointestinal sensations, and the emotions cannot be discounted. On the other hand, while these phenomena are of importance in that they exert a modifying, if usually temporary, effect on food intake, they clearly cannot begin to account for the long-term quantitative aspects of food intake regulation.

These "accessory" considerations assume less and less importance as caloric intake is increasingly restricted. This fact seems to be well illustrated in the case of A. G. (Experiment 2—Constant Inadequate Caloric Intake). The small meal he had at noon failed

to alleviate his hunger even temporarily (Fig. 1).

The influence of cortisone on glucose utilization as shown in Experiment 4 (Fig. 2) is of particular interest. The stimulating effect of cortisone on appetite was commented upon by Hench *et al.* in an early study.[19] Patients receiving cortisone frequently gain weight not accounted for by water retention. Patients with Cushing's syndrome become obese. One possible explanation for the appetite-enhancing effect of cortisone may be found in its inhibitory action on peripheral glucose assimilation, and the accompanying metabolic hypoglycemia which ensues to a varying degree. Despite the higher levels of blood sugar which obtain after cortisone is administered, the Δ-glucose area (which best reflects glucose utilization[20]) is much smaller during the day of cortisone administration in Experiment 4 (Fig. 2) than during the control day.

"Starvation," uncontrolled diabetes mellitus, and cortisone hyperglycemia all display a diminished Δ-glucose area; these three conditions also may be accompanied by excessive hunger, and in the last two instances, polyphagia. This suggests that situations in which phosphorylation of glucose is impaired are likely to be associated with increased desire for food. Thus, although uptake of glucose in the central nervous system generally is not subject to hormonal influence, there may be receptors concerned with food intake regulation that are. If this were not the case, the patient with uncontrolled diabetes mellitus might be expected to suffer from constant anorexia rather than polyphagia.

A Δ-glucose which is at or near zero signifies a level of arterial blood sugar which at that time is below the "threshold" necessary for ingress of glucose into cells. Non-nervous tissues adapt to metabolic hypoglycemia by oxidizing an increasing proportion of fat. However, the central nervous system depends largely on glucose for its energy needs,[11] and thus hunger as one of the consequences of carbohydrate deprivation would appear to be a crucial homeostatic response.

The effect of insulin on appetite may appear to be inconsistent, in this scheme, with its action in temporarily increasing peripheral utilization of glucose and thereby increasing arteriovenous glucose differences. However, Somogyi[21,22] has shown that there are two metabolic phases in the response to insulin administration; the first is a fall in blood sugar due to increased peripheral utilization of glucose; the second is a compensatory rise secondary to decreased utilization of glucose in the periphery. That decreased utilization occurs is shown by the rapid decline in Δ-glucose values to zero which occurs as the blood sugar falls to or below postabsorptive levels. Somogyi interprets this as a defensive response to hypoglycemia by the pituitary-adrenal endocrine "axis," in which hormones antagonistic to insulin action are released in increasing amounts.

Thus, hunger as a consequence of insulin administration is not inconsistent with its role as part of the system of homeostatic defenses against metabolic hypoglycemia. Some of these defenses manifest themselves as the second phase of the metabolic response to insulin administration.*

In hyperthyroidism, alimentary hyperglycemia typically occurs and is followed regularly by a postalimentary hypoglycemia. Peters and Van Slyke[23] believe that accelerated metabolism of glucose may take place in the hyperthyroid patient and that the alimentary hyperglycemia may be only a manifestation of starvation diabetes following rapid depletion of carbohydrate stores. It is interesting to consider whether the metabolic hypoglycemia which is said to occur readily in hyperthyroidism can be etiologically related to the increased food intake characteristic of this condition.

In conclusion, the findings described in this paper lend support to the view that the urge to eat is a homeostatic response to carbohydrate deprivation. By this interpretation, decreased intake of dietary precursors of glucose, decreased assimilation of circulating glucose by cells, or abnormally increased oxidation of glucose, all may be considered to have

* This phenomenon has since been studied in detail in alloxan-diabetic animals (Mayer and Bates, in press).

in common some degree of metabolic hypoglycemia resulting in an increase in desire for food.

Summary

Blood sugar studies were done on six adult human subjects either under "metabolic balance" conditions or when food intake was carefully recorded. Six experimental situations were investigated: (1) constant adequate caloric intake, (2) constant inadequate caloric intake, (3) uncontrolled diabetes mellitus, (4) cortisone administration, (5) low fat diet, and (6) epinephrine administration.

An attempt was made to correlate various dietary regimens, arteriovenous glucose differences (Δ-glucose) and presence or absence of an urge to eat.

In normal subjects, values for Δ-glucose throughout the day generally reflected the previous dietary intake. A submaintenance caloric intake was associated with a small Δ-glucose area and an adequate caloric intake with a normal Δ-glucose area.

Cortisone administration was followed by hyperglycemia but a smaller than normal Δ-glucose area. The effect of cortisone on food intake was interpreted in the light of this finding.

It is believed that consideration of the antecubital Δ-glucose area as an index of glucose assimilation by peripheral tissues permits application of the glucostatic theory to conditions associated with impaired carbohydrate utilization.

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RESUMEN

Diferencias de la glucosa arteriovenosa, hipoglucemia metabólica e ingestión de alimentos en el hombre

Se realizaron estudios de glucemia en 6 individuos adultos, sujetos a las condiciones de "balance metabólico" o registrando cuidadosamente los alimentos ingeridos. Se investigaron 6 situaciones experimentales: (1) ingestión calórica adecuada constante, (2) ingestión calórica inadecuada constante, (3) diabetes mellitus no controlada, (4) administración de cortisona, (5) dieta pobre en grasa, (6) administración de epinefrina.

Se intentó establecer una correlación entre diversos regímenes dietéticos, las diferencias de glucosa arteriovenosa (Δ-glucosa) y la presencia o ausencia del deseo de comer.

En los sujetos normales los valores de Δ-glucosa durante el día reflejieron, en general, la ingestión alimenticia previa. La ingestión insuficiente de calorías estuvo asociada a un área de Δ-glucosa pequeña, y una ingestión de calorías adecuada a un área de Δ-glucosa normal.

La administración de cortisona fué seguida de hiperglucemia, pero de un área de Δ-glucosa inferior a la normal. El efecto de cortisona sobre la ingestión de alimentos fué interpretado a la luz de este hallazgo.

Se cree que la consideración del área antecubital de Δ-glucosa, como índice de la asimilación de glucosa por los tejidos periféricos, permite la aplicación de la teoría glucostática a las condiciones asociadas con una utilización defectuosa de los hidratos de carbono.

Take Your Choice

"We have never known the slightest ill-result from the strictest dieting of a child. On the contrary, we emphasise that no child who is obese from any cause should be allowed to take an unrestricted diet, because the benefit of weight reduction is so great. It is sometimes said that the dieting of small children is unnecessary because they will get normal without treatment at some later date, e.g., puberty or adolescence. There is no general rule of this kind. Spontaneous cure is very uncertain and dieting should be adopted as soon as the child is seen whatever the age."
—H. S. Le Marquand. *The Medical Press* 228: 485, 1952.

"No child should be dieted. If he is too fat it probably is due to an endocrine disturbance in the treatment of which diet will play little or no part. The child who is too fat merely from overeating never should be given a diet and never, never drugs. His fat is a symptom that his parents are bringing him up badly; if this can be altered he will get thinner, if it cannot be altered he will remain fat."
—F. Bicknell. *The Medical Press* 228: 493, 1952.

Early to Grow, Early to Die?

"Speculation, and it can be little more at present, starts with the well-known findings of McCay and others that in rats a limitation of caloric intake during growth leads to a significant increase in the life span. The finding is significant in several ways, even though it is by no means clear how much if any of it can be applied to man. It must, however, lead to a consideration of the advisability of 'forcing' the nutrition of children. There has long been before us the possibility, if nothing more, of a deleterious effect of disproportionately good nutrition or intake of some nutrient on the nutritional status of the others, i.e., the production of a deficiency of one nutrient because of the excess intake of another.... Whether simple abundance of calories, permitting greater and more rapid growth, may cause changes to be reflected in earlier senescence, is unknown. However, in view of the changing incidence of certain degenerative diseases, the possibility must be kept in mind."
—J. B. Youmans. *Journal of the American Dietetic Association* 28: 1032, 1952.

The Use of ORAL HIGH FAT, HIGH CALORIE EMULSION *for Total Feeding*

By W. James Kuhl, Jr.,* Morton I. Grossman,† and C. Frank Consolazio‡

While restricted to a liquid diet, the maintenance or restoration of body weight, a positive nitrogen balance, and an adequate caloric, mineral and vitamin intake have in the past been achieved only with some difficulty. Recent studies[1-4] have indicated that fat emulsions can be readily used as a source of available calories. According to these reports, the desirable features of the emulsions include ease of handling and mixing in liquid preparations, good stability at the usual temperatures of storage, and a relatively high acceptance of the preparation when combined with suitable flavoring agents. This study was undertaken to determine if a high calorie, high fat liquid feeding could be administered to selected patients as the sole source of feeding, and if this would be accompanied by gain in weight, restoration of positive nitrogen balance, and minimal alteration in normal metabolism.

Experimental Methods and Procedures

Six patients with fracture of the mandible and wiring were followed with metabolic studies. All had lost weight prior to the initiation of the study. All received a high calorie liquid feeding, consisting primarily of a 40 per cent emulsion of peanut oil[§] which supplies 4.0 cal. per ml. This was prepared by combining a protein concentrate[**] with the emulsion and adding sodium chloride, iron, and ascorbic acid in order to include the daily requirements of electrolytes, minerals, and vitamins. In the preparation 100 Gm. of the protein concentrate, which also contained many vitamins and minerals, was added to 1000 ml. of the fat emulsion. One hundred mg. of ascorbic acid, 4.0 Gm. of sodium chloride as a normal saline solution, and 85 mg. of iron as ferric ammonium citrate were added, and the preparation mixed in a blender. This was then refrigerated until consumed. Five of the patients consumed the arbitrarily determined amount of 1000 ml. of the fat emulsion and supplements daily in divided feedings, providing 4370 cal. The sixth patient varied his daily intake over the period of study, beginning with a smaller amount of the preparation, consuming the fixed amount of 1000 ml.

From the U. S. Army Medical Nutrition Laboratory and the Hektoen Institute for Medical Research, Chicago, Illinois.

* 1st Lt., M.C., Clinical Investigation Division.

† Capt., M.C., Clinical Investigation Division.

‡ Biochemistry Division.

§ Lipomul, Oral (Upjohn), a 40 per cent emulsion of peanut oil, with 10 per cent dextrose, 2 per cent purified soybean phosphatide, and 0.2 per cent synthetic emulsifier (alkylarylpolyether alcohol). One thousand ml. of this emulsion contains 200 mg. sodium, 250 mg. potassium, 140 mg. chloride, 50 mg. calcium, and 600 mg. phosphorus.

** Somagen (Upjohn), 100 Gm. contains 70 Gm. milk protein, 22 Gm. dextrose, 150 mg. sodium, 1.40 Gm. potassium, 1.20 Gm. chloride, 1.40 Gm. calcium, 1.0 Gm. phosphorus, 5 mg. thiamine, 5 mg. riboflavin, 2 mg. pyridoxine, 10 mg. calcium pantothenate, 30 mg. nicotinamide, 2 mg. folic acid, 2 Gm. liver concentrate, and yeast extract from 15 Gm. yeast.

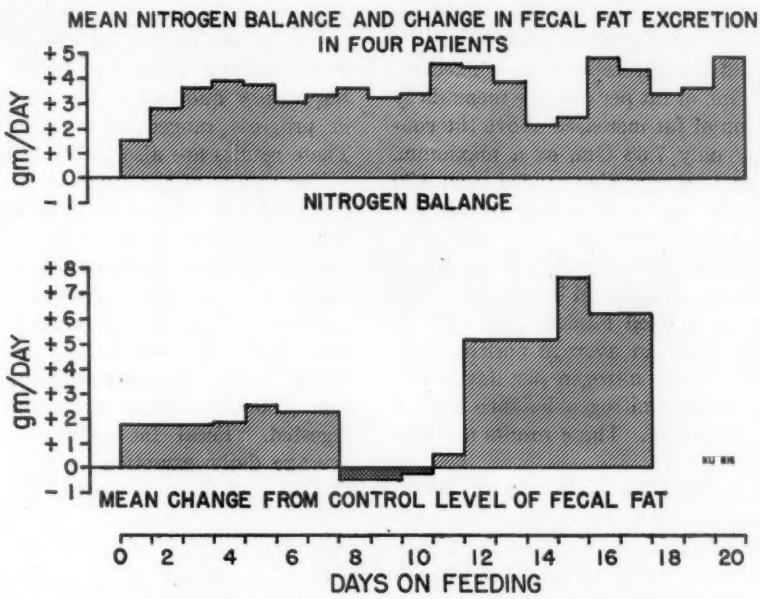

Fig. 1. Mean nitrogen balance and change in fecal fat excretion in four patients.

for seven days, then further increasing his intake.

All patients were weighed daily and control weights were recorded for a period preceding and following the feedings. Each patient reported all changes in bowel habits and subjective changes in appetite, digestive symptoms, and strength. The following determinations were made at the intervals noted: urine volume and nitrogen excretion,[5] daily; urinary ketones[6] and urobilinogen,[7] semi-weekly; fecal nitrogen[5] and fat[8] excretion, 3–5 day collections; blood total and neutral fat,[9] phospholipid,[10] CO_2 content,[11] non-protein nitrogen,[12] fasting blood sugar,[13] weekly; serum total protein[5] and A/G ratio,[14] free and total cholesterol,[15] sodium,[16] potassium,[17] and chloride,[18] weekly; basal metabolic rate and respiratory quotient by collection of expired air with a Douglas bag under basal conditions and analysis in the Haldane apparatus, weekly.

Results

The results obtained with the first five patients studied are summarized in Table I and Figure 1. The results on the sixth patient are presented separately, since he did not consume the fixed daily amount of the emulsion and hence had a variable daily caloric, mineral, and vitamin intake.

All five of the initial patients gained weight while on the fixed intake of 1000 ml. of fat emulsion in a complete feeding. The weight gain ranged from 2.75 to 12.25 lb. in a period of from 12 to 24 days, or an average of 7.6 lb. in 18.8 days. The average daily weight gain per 1000 ml. of fat emulsion was 0.4 lb. All patients noted an increase in strength and four noted an increase in appetite. Two patients developed symptoms of intolerance and were

TABLE I

	Number of patients	5
	Average age	36
Average daily total intake	Carbohydrate, Gm.	122
	Protein, Gm.	70
	Fat, Gm.	400
	Calories	4368
Average number of days		18.8
Average daily intake of emulsion, ml.		1000
Average daily calories from emulsion		4000
Number of patients gaining weight		5
Average weight gain, lb.		7.6
Number of patients losing weight		0
Average weight loss, lb.		0

not suitable for metabolic studies; their results are not included in this report.

While the five subjects were on a fixed intake of 400 Gm. of fat per day the mean daily fecal excretion of fat increased above the control level by only 7.68 Gm. as a maximum. The daily fecal fat excretion ranged from 2.20 to 24.8 Gm. per day, or from 0.55 to 6.20 per cent of the amount ingested. The results in four subjects are shown in Figure 1. All of the patients were maintained in positive nitrogen balance on a fixed intake of 70 Gm. of protein daily, with an average positive balance of 3.46 Gm. of nitrogen per day. The mean daily positive nitrogen balance ranged from 1.39 to 5.04 Gm. These results are also shown in Figure 1.

In all six patients the weekly fasting blood studies revealed no increase in total fat, neutral fat, phospholipid, or cholesterol. There was no consistent change in serum total protein, A/G ratio, N.P.N., fasting blood sugar, CO_2 content, sodium, potassium, or chloride. All determinations of urine urobilinogen remained within normal limits. Urinary ketones were only occasionally detectable in trace amounts, and disappeared with increased fluid intake. These results are shown in Table II.

All of the B.M.R. determinations remained within normal limits, but apparently increased slightly within these limits initially during the course of the feeding of the individual, and then returned to control levels. The mean respiratory quotient while the feedings were in progress ranged between 0.76 and 0.83. These results are also in Table II.

TABLE II

Days on feeding	Control	Days 7–10	Days 15–17	Days 20–24
No. of subjects	5	5	4	2
Esterified fatty acid, total mEq./L.	11.71	7.59	8.55	10.33
Phospholipid phosphorus, mg. per 100 cc.	7.12	6.01	5.63	7.32
Cholesterol, total, mg. per 100 cc.	189.	122.	157.	177.
CO_2 content, Vol. per 100 cc.	61.7	58.5	63.4	63.6
Non-protein nitrogen, mg. per 100 cc.	42.0	37.4	35.3	39.0
Fasting blood glucose, mg. per 100 cc.	56.0	64.5	63.0	72.0
Total serum protein, Gm. per 100 cc.	7.12	7.18	7.35	7.05
B.M.R.	+3	+14	+1	+2
R.Q. (respiratory quotient)	0.80	0.75	0.83	0.76

The results of the study of the last patient are shown in Figure 2. During the period when he was consuming 1000 ml. or more of the fat emulsion and supplements there was a slow gain in weight. As the intake was increased, nitrogen balance became positive and more fluid was retained. This can be seen readily on day 15 when 1500 ml. of the emulsion (600 Gm. of fat) and supplements were ingested. Fecal fat attained a maximum average daily excretion of 6.71 Gm. during the last nine days of study.

Discussion

The attainment of a markedly positive nitrogen balance while on a total daily intake of 70 Gm. of protein further confirms the well-known effect of increased caloric intake upon nitrogen balance. Previous workers[19–21] have shown that without change in daily protein intake, nitrogen balance can be converted from negative to positive by caloric supplementation. The use of fat emulsion in this study has made practicable the administration of a high caloric liquid diet. Previous studies have shown little change in fecal fat on diets containing 100 to 200 Gm. of fat per day;[22–24] however, there are only a few studies on diets containing over 300 Gm. of fat per day.[25] While the protein intake might be decreased and nitrogen balance continue to be positive if the caloric intake remained at high levels, further studies are needed to determine the minimal amount of protein intake which is necessary to keep these patients in positive balance while on this caloric intake.

It is of interest that none of these patients had an increase in their fasting blood levels of total or neutral fat, phospholipid, or cholesterol. The lack of an increase in cholesterol while on a high daily fat intake is of particular interest in view of recent reports[26,27] that dietary fat restriction is necessary in order to effect a decrease in the elevated chol-

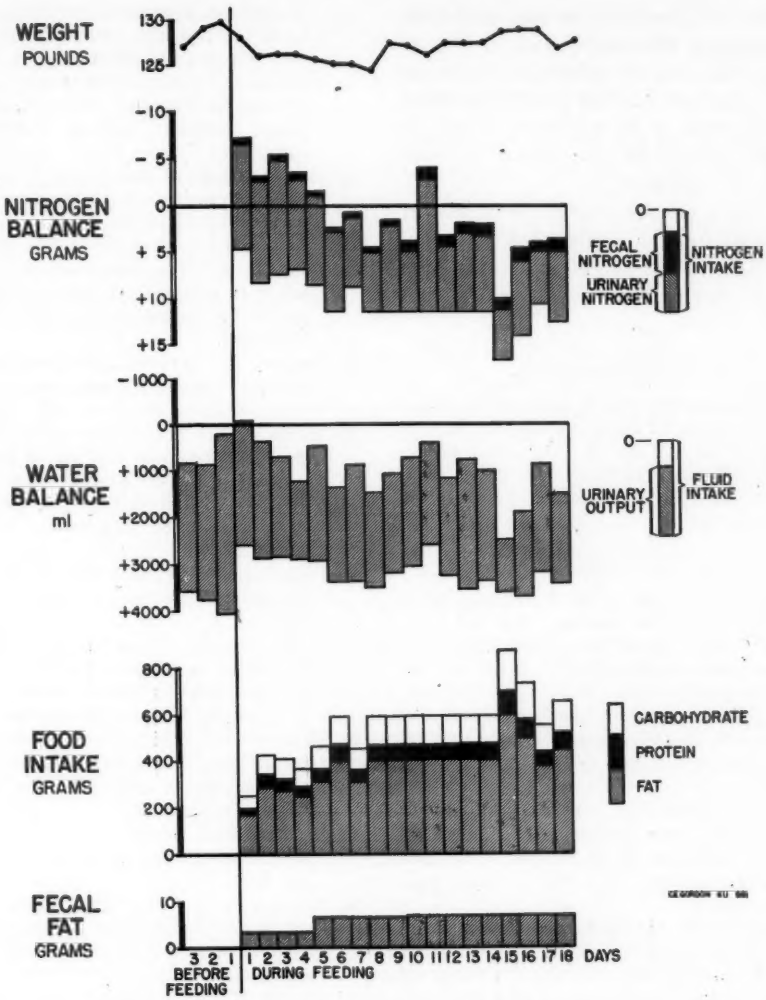

Fig. 2. Balance studies on patient F. R.

esterol levels observed in some diseases.

Intolerance to fat emulsion is a major difficulty, with nausea, vomiting, and diarrhea or constipation as the most frequently encountered symptoms. In some patients the onset of these symptoms is apparently unrelated to the size of the dose ingested and not correlated with demonstrable gallbladder disease. With prolonged ingestion, as in this study, the monotony of flavor becomes a problem in some patients, but the use of a chocolate flavor usually obviated this difficulty.

Another difficulty in the use of the emulsion is that, although stable when stored at ordinary temperatures, gradual separation of the fat occurs after the emulsion has been mixed with protein concentrate and electrolytes. After storage with refrigeration for from 30 to 48 hours, this separation necessitates the discarding of the mixture, and makes daily preparation of the mixture advisable.

Summary

A high calorie liquid diet, consisting primarily of a 40 per cent fat emulsion, was administered as the sole source of feeding to

six patients with fracture of the mandible.

While ingesting 400 Gm. of fat, 70 Gm. of protein, and 122 Gm. of carbohydrate, an increase in weight and marked positive nitrogen balance was noted in all subjects. Fecal fat excretion increased 7.68 Gm. above the control level as a maximum.

No consistent changes occurred in fasting blood levels of total or neutral fat, phospholipid, cholesterol, serum total protein or A/G ratio, N.P.N., fasting blood sugar, or CO_2 content.

Acknowledgment

This study was carried out in conjunction with a study with Dr. Irving F. Stein, Jr., and Dr. Edward M. Goldberg on the oral use of fat emulsion in surgical patients, the results of which were presented at the New York Academy of Sciences, Conference on Oral Fat Emulsions[25].

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Resumen

El empleo de una emulsión oral rica en grasa y en calorías para la alimentación total

Una dieta líquida rica en calorías, constituida principalmente por una emulsión de 40 por 100 de grasas, fué administrada como única fuente alimenticia a 6 pacientes con fractura de mandíbulo.

Mientras injerían 400 grs. de grasa, 70 grs. de proteina, y 122 grs. de hidratos de carbono, se notó en todos los sujetos un aumento de peso y un marcado balance positivo de nitrógeno. La excreción de grasa en las heces aumentó 7,68 grs. por encima del nivel de control, como máximo.

No se produjeron cambios uniformes en los niveles sanguíneos, en ayunas, de la grasa total o neutra, de los fosfolípidos o del colesterol, de las proteinas totales del suero, del cociente Alb/Glob., del nitrógeno no-protéico, de la glucemia en ayunas, o del contenido de CO_2.

Curiosity and Mystery

"Only children and philosophers seem interested in why ordinary things are, rather than are not. The rest of mankind is too busy with its real and little affairs to listen to their metaphysical questions or those of nature. Not only extraordinary deaths and marvelous cures but all the predicaments of patients, whether horrible or pleasing, in the thoughtful and detached view, beget a lively awareness of the mystery at the heart of being and lend devoutness to the traditional confession of faith: 'We dress the wound, God heals it.'"
—Editorial: On Extraordinary Deaths and Marvelous Cures. *New England Journal of Medicine* 247: 1045, 1952.

Fat and Fashion

"In former generations, judging by literary evidence, a moderate degree of obesity was scarcely regarded with distaste. It would probably be going too far, of course, to say that we have ever approached the attitude of the Chinese, who apparently regard fatness not only as desirable in itself because of the well-being, or the alleged well-being it implies, but also as an outward and very visible sign of prosperity and success in life. What is the use, ask the Chinese, of being rich if you are not also fat? And in a country in which starvation is endemic the question is not so absurd as it might appear. To-day in this country such an attitude would border on heresy."
—Editorial. *The Medical Press* 228: 471, 1952.

Complications of Dietary Calculations

"Of course the list of permitted vegetables can be endlessly enlarged, but the patient will pay too heavily for the pleasure of eating, for instance, red-peppers if he has to memorise a long list, especially as he will forget it and honestly believe it includes sweet corn. Again bread and potatoes may be exchanged for the right amount of any prohibited food but neither doctors nor patients have the time to remember that one ounce of bread equals three ounces of boiled macaroni, two and a half ounces of boiled lentils, or three quarters of an ounce of uncooked rice. Unemployed hypochondriacs can buy their own food tables and weigh all their food, though it will drive their families mad."
—F. Bicknell. *The Medical Press* 228: 492, 1952.

EFFECT UPON SERUM CHOLESTEROL *and* PHOSPHOLIPIDS *of* DIETS CONTAINING LARGE AMOUNTS OF VEGETABLE FAT

By LAURANCE W. KINSELL, M.D., GEORGE D. MICHAELS, PH.D., JOHN W. PARTRIDGE, M.D., LENORE A. BOLING, M.D., HARRY E. BALCH, M.D., AND GILBERT C. COCHRANE, M.D.

With the technical assistance of MARJORIE COELHO, GEORGE FUKAYAMA, FLORENCE OLSON, AND SADIE SMYRL

THE RELATIONSHIP of dietary constituents to the level of serum lipids and to the atherosclerotic process has been a subject of controversy for many years. It has been stated that not only dietary cholesterol *per se* is of importance in the determination of serum cholesterol levels, but that diets containing little or no cholesterol but large amounts of fat will also result in relative or absolute elevation of serum cholesterol.[1-3]

The present study reports the findings in a group of patients studied on the metabolic ward and maintained on chemically constant formula diets over a prolonged period. Excepting only the "pure fat" diets, the patients were maintained in weight equilibrium and excellent nutrition including a positive nitrogen balance.

METHODS

In each instance the diet was administered as a formula, usually through a tube, the tip of which lay in the stomach or duodenum. Dietary composition was constant in a quantitative sense. Salad oil composed of cottonseed oil alone, or of mixed soy and cottonseed served as the source of vegetable fat. Calcium caseinate* was the protein source. The formulae were fortified with adequate amounts of minerals and vitamins.

Free and total cholesterol were determined by a modification of the method of Schoenheimer and Sperry.[4] Phospholipids were assayed by the method of Youngburg and Youngburg.[5] In most instances, protein balance studies were carried out simultaneously.

FINDINGS

The first patient so studied (Fig. 1) was maintained on a diet in which, for a period of 30 days, all of the calories were supplied in the form of an emulsion of vegetable fat. The primary purpose of the study was to determine the effect of corticotropin and cortisone upon certain aspects of fat oxidation.[6] In the course of this study, it was noted that a rather profound fall occurred in the levels of serum cholesterol and phospholipids, the greater portion of the cholesterol fall being in the ester fraction. Initially, it was assumed that this fall was referable to the co-administration of hormonal therapy.[7]

A later study, carried out in a patient with combined acromegaly and diabetes and maintained on a formula diet containing only fat and protein (Fig. 2), revealed a fall in total cholesterol from approximately 300 to 200

From the Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

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* Furnished through the courtesy of Mead Johnson and Company.

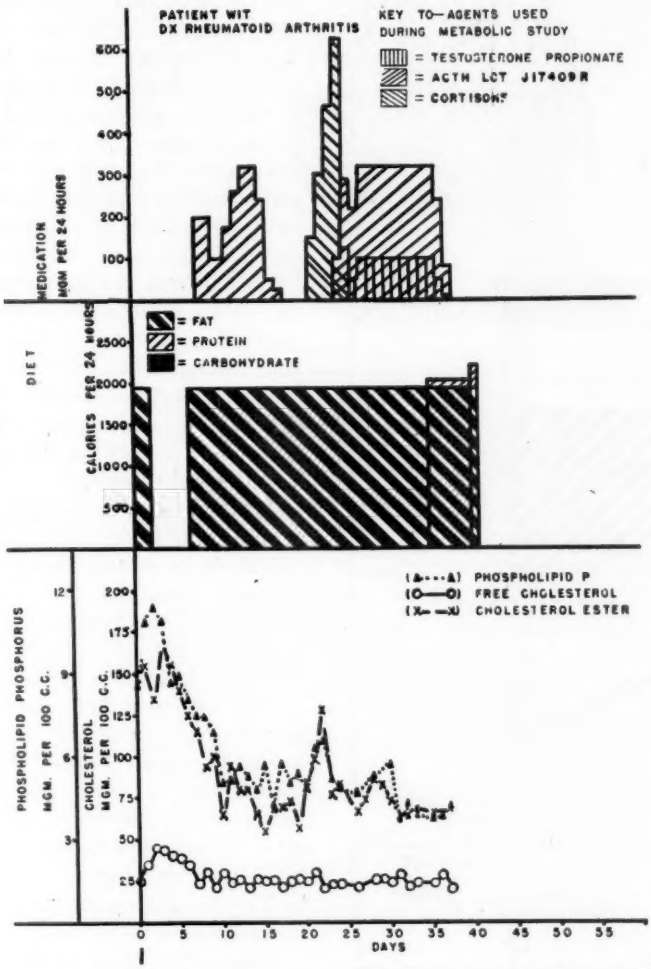


Fig. 1. Major fall in plasma cholesterol esters and phospholipids in a patient maintained on a "pure fat" formula intake. Initially it was assumed that ACTH therapy was responsible for this fall.

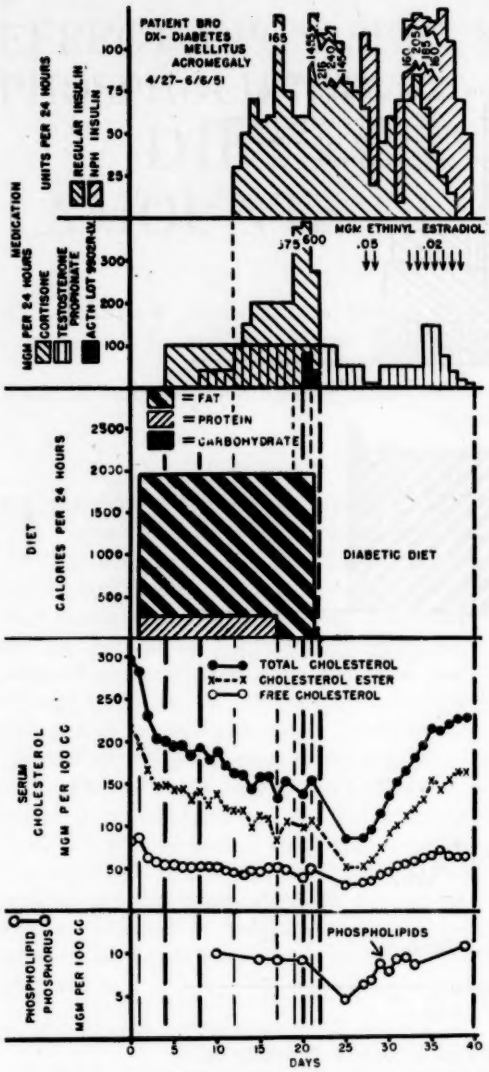


Fig. 2. Fall in plasma lipids during high vegetable fat intake. *The greater portion of the fall occurred prior to hormonal therapy.* A mixed diet resulted in return of lipids toward their previous levels.

mg. per cent in the space of four days, prior to the institution of any hormonal therapy. A further fall occurred with continuation of the diet and during the administration of hormonal therapy as noted in Figure 2. With resumption of a "standard" relatively high fat diabetic diet, and continuation of a portion of the hormonal therapy, the serum lipids rose toward the values which were obtained prior tc the institution of the vegetable fat diet. This raised the question as to whether the formula diet *per se* might be responsible for the rather striking fall in cholesterol.

The next patient studied was maintained on an average mixed diet for a period of 15 days, after which the diet contained only fat and protein except for a brief period as shown (Fig. 3). With the institution of the high vegetable fat formula diet, her cholesterol levels fell from average values of 150 to average values of 75 mg. per 100 cc. The phospholipids behaved in a less constant fashion. The addition of as much as 60 Gm. daily of cholesterol to the diet resulted in no significant elevation of serum cholesterol, despite the absorption of approximately 50 per cent of the administered cholesterol (as indicated by determination of total digitonide precipitable sterols in the feces).

A study carried out in a patient with thyrotoxicosis, prior to the institution of any therapy and maintained on a formula diet which was compatible with excellent nutrition and weight equilibrium, resulted in a fall in serum cholesterol from average levels of approximately 120 mg. per 100 cc. to levels as low as 50 mg. per 100 cc. A proportional fall occurred in the phospholipids. With the resumption of a mixed diet, and despite continuation of hormonal therapy (which was instituted in the mid-portion of the study as shown in Fig. 4), the serum lipid levels rose to or above their initial value.

A similar study in a patient with untreated myxedema revealed a fall in serum total cholesterol from values averaging 220 mg. per cent to values below 100 mg. per cent. A comparable fall in phospholipids occurred (Fig. 5).

A later study in a patient maintained for a prolonged period of time on diets in which vegetable and animal fat were alternated in calorically equivalent amounts for specific periods, revealed findings comparable with the preceding, that is, a fall in cholesterol and phospholipids on the vegetable fat intake, and a rise to average levels on formula diets in

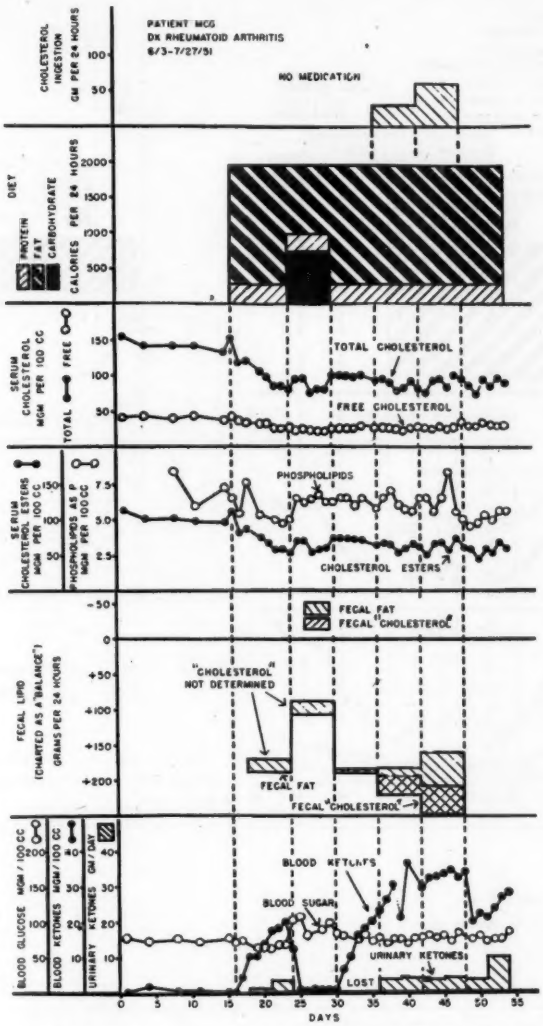
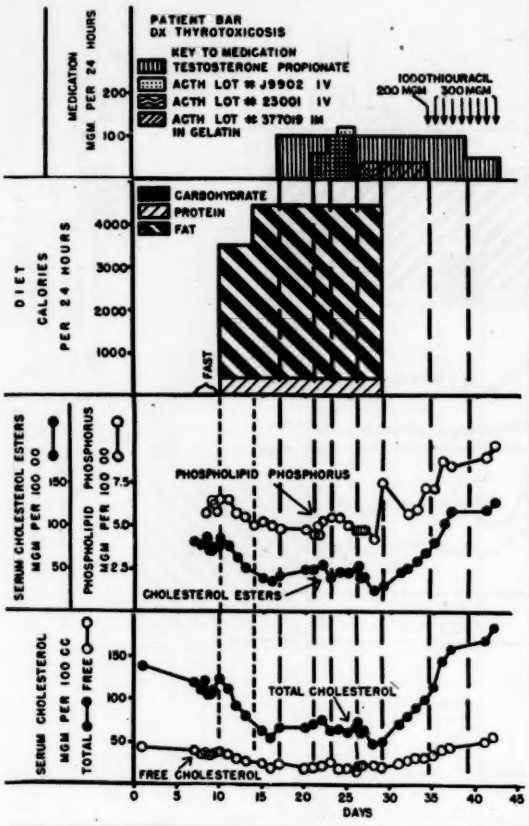


Fig. 3. Fall in serum lipids on high vegetable fat intake. Cholesterol administration caused no maintained elevation of lipids, despite evidence of absorption of approximately 50 per cent of the administered cholesterol (fecal "cholesterol" includes *all* digitonide precipitable lipids).

which the fat was entirely of animal origin. During a portion of this study the fat was derived entirely from egg yolk in an amount equivalent to 36 egg yolks daily. Normal but not supernormal levels of cholesterol occurred during the egg yolk feeding (Fig. 6).

More than twenty studies of the type noted above have been carried out on the metabolic ward in this institution. Included among the patients are relatively normal individuals, patients of the types noted above, and others with initial hypercholesterolemia in association with severe diabetes and with the nephrotic syndrome. A study in one such nephrotic is shown in Figure 7. A major fall in the cholesterol and phospholipids occurred on diet



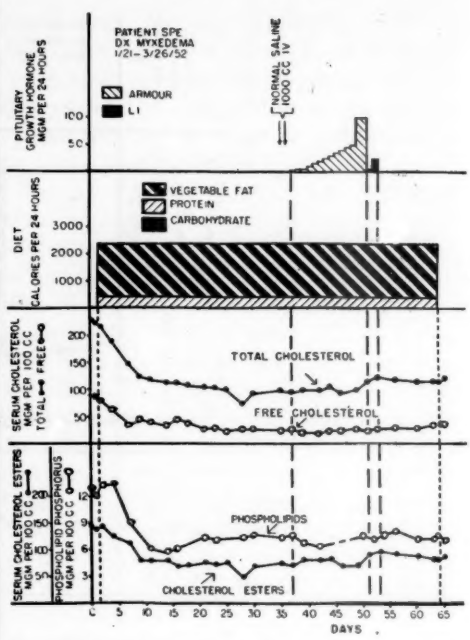


Fig. 4. (left). High fat diet-induced fall in plasma lipids in a hyperthyroid patient.

Fig. 5. (above). Fall in plasma lipids in a myxedematous patient during intake of a high vegetable fat diet.

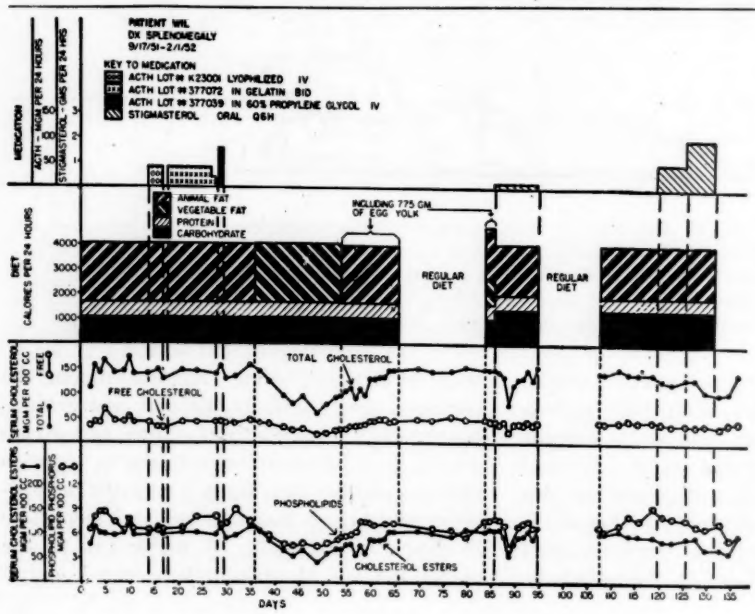


Fig. 6. Effects of calorically equivalent amounts of animal and vegetable fat upon plasma lipids. Egg yolk equivalent to 36 eggs daily did not result in "hypernormal" cholesterol levels. The effect of stigmasterol may or may not be significant.

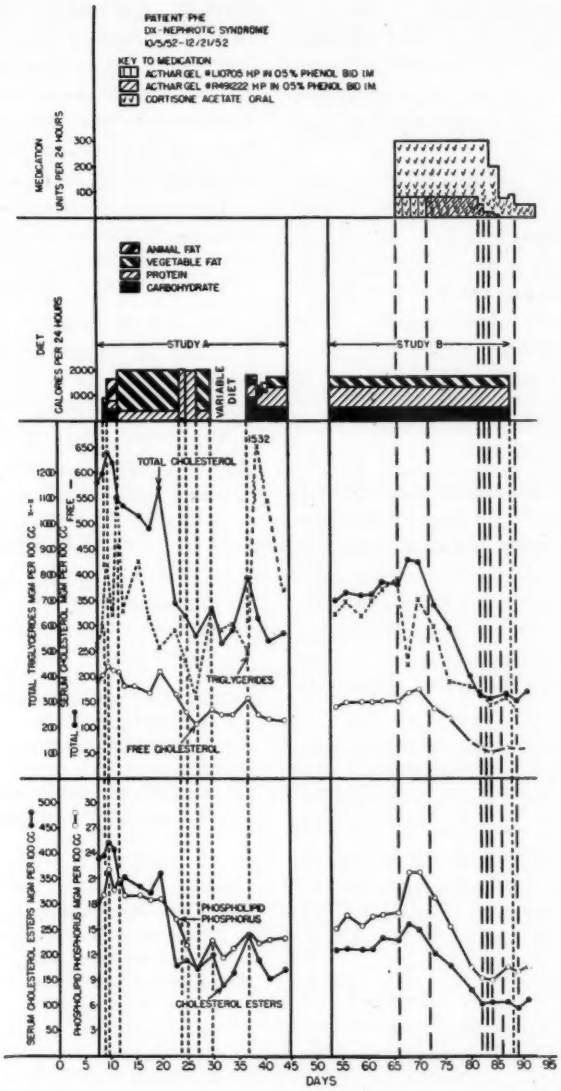


Fig. 7. Effect of a high vegetable fat diet upon a nephrotic patient with marked elevation of serum lipids. Because of the onset of nausea and vomiting, it was impossible to continue the high fat formula. It is of interest that during the diet-induced fall in serum lipids, no change in serum protein occurred; whereas, during the ACTH-cortisone-induced remission of the disease, a rise in serum albumin and a fall in serum globulin occurred in association with the decrease of serum lipids to normal levels.

alone. Because of the appearance of nausea and vomiting, it was impossible to continue the high vegetable fat diet in this patient. The serum lipid values did not return completely to normal until the nephrotic syndrome was completely controlled with ACTH and cortisone therapy.

The findings in the severe diabetics with elevated serum lipids will be reported in detail in a separate communication. In all instances, the institution of diet high in vegetable fat and in protein has resulted in a major fall in cholesterol and phospholipids. The fall in the two entities has usually been proportional, although occasional exceptions to this have been noted.

Discussion

From the foregoing, it appears that patients maintained on chemically constant diets containing very large amounts of fat of vegetable origin, without exception have striking falls in plasma cholesterol and usually in phospholipids. The precise metabolic and clinical interpretation of these findings is by no means clear, but the following statements appear to be in order:

1. Formula diets containing large amounts of fat in which all of the fat is of vegetable origin (that is, essentially free of cholesterol) are associated with a profound fall in the serum lipids above noted. This would appear to refute the statements which appear in the literature that high dietary fat *per se* is always associated with relative or absolute elevation of serum cholesterol.

2. The reason for the fall in cholesterol and phospholipids under the conditions above reported is unknown. The following possibilities must be considered:

(a) The findings are referable merely to the lack of dietary cholesterol and phospholipids.

(b) Some component of the vegetable fat, possibly one or more of the vegetable sterols, has some direct or indirect effect upon cholesterol and/or phospholipid metabolism. Peterson has reported that the administration of soybean sterols has such an effect, but feels that the mechanism is largely one of interference with absorption.[8]

(c) Some other component of the fat formula is responsible for the observed effect. In this connection it should be noted that the formula diets have been emulsified with either a cerebroside preparation,* or Tween 80® (polyoxyethylene (20) sorbitan monoöleate).† The effects observed, however, do not appear to depend upon the emulsifier which is used.

The above possibilities are currently under investigation.

Summary

The use of formula diets containing large amounts of vegetable fat has resulted consistently in a major fall in serum cholesterol and in phospholipids. Whatever the meaning of this observation, it is apparent that high dietary fat *per se* does not result in elevation of serum cholesterol.

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* Furnished through the courtesy of Dr. Edwin Hays of the Armour Laboratories.

† Furnished through the courtesy of Mr. C. D. Pratt of Atlas Powder Company.

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Resumen

Efecto de dietas ricas en grasas vegetales sobre el colesterol y los fosfolípidos séricos

El empleo de fórmulas dietéticas ricas en grasas vegetales ha resultado constantemente en un descenso importante de los niveles del colesterol y los fosfolípidos séricos. Cualquiera sea el significado de esta observación, es evidente que las dietas ricas en grasa no conducen por sí mismas a una elevación del colesterol sérico.

Cocktails and Calories

"Cider, wine, gin and cocktails must be forbidden: even a dull cocktail party may provide about three quarters of the entire day's ration of calories. For those whose business leads them to bars and dinners, tomato juice—that most repellent of all drinks—seems to be accepted as a 'good fellow' drink. While at parties beer surreptitiously used to replace sherry in a sherry glass can camouflage the social solecism of sobriety."
—F. Bicknell. *The Medical Press* 228: 493, 1952.

Meat Exonerated

"The conviction is more widespread than one might think that meat causes vascular diseases, arterial hypertension, intoxications and uremia.

"This is at variance with scientific reality: the newer concepts of the pathogenesis of arteriosclerosis, in fact, attribute much greater importance to lipid metabolism, especially to cholesterol levels, than to protein metabolism. It may be recalled here that the much vaunted vegetarian diet is no protection against vascular sclerosis, to judge from the diffusion of this disease among the Hindu population which lives solely on milk, eggs and cereals, and among herbivorous animals like the horse.

"Nor is it true that meat, in proper proportions, is any more responsible for intoxications than other animal proteins may be, and the treatment of arterial hypertension today depends more on a diet low in sodium than in proteins. It thus remains inexplicable that meat, and not fish, should be blamed for damage through an excess of uric acid, when both contain approximately the same amount of uric acid; sardines, in fact, are richer in it."
—D. Jasonni. *Archivio Italiano delle Malattie dell'Apparato Digerente* 18: 294–295, 1952.

The Original Description of Rickets

The Signs which belong to the disproportioned nourishment of the parts.

First, there is an unusual Bigness of the Head.

Second, the fleshy parts are daily more and more worn away.

Third, certain swellings and knotty excrescences are observed about some of the joynts.

These are chiefly conspicuous in the wrists, and somewhat less in the ankles. The like tumors also are in the tops of the Ribs, where they are enjoyned in the gristles in the Breast.

Fourthly, some bones wax crooked, especially the bone called the shank bone, and the Fibula or small bone of the leg.

Fifthly, the Teeth come forth both slowly and with trouble.

Sixthly, the Breast in the higher progression of the disease becomes narrow on the sides.

—Francis Glisson (from *De Rachitide*, Batavia, 1650)

Review: The Fundamentals of CLINICAL PROTEINOLOGY

By Co Tui, M.D.

Clinical proteinology may be defined as that branch of protein study which has to do with clinical conditions. General protein study, which we may term general proteinology, dates from 1839, when Mulder[1] originated the term *protein*, from the Greek word *proteos*, meaning "of first importance," because these organic substances are the universal component of all living tissues, vegetal as well as animal, and "unquestionably the most important of all known substances in the organic kingdom. Without it no life appears possible on our planet. Through its means the chief phenomena of life are produced." This statement adumbrated the protein research of the last century, during which proteinology has become almost coextensive with biology itself—incidentally demonstrating the keenness and accuracy of Mulder's scientific insight.

Three years after Mulder's work became known, Liebig[2] suggested that the nitrogen in the urine might serve as an indicator of protein destruction in the body. Bidder and Schmidt[3] in 1852 applied this method systematically to determine the urinary nitrogen excretion of meat-fed dogs and cats. But it was not until 1857 that Voit[4] established the validity of the nitrogen equilibrium. From then on, the study of the nitrogen metabolism of normal humans and animals was carried forward, principally by Voit himself, by Rubner,[5] and, in this country, by Chittenden[6] and Mendel.[7]

Clinical proteinology may be said to begin with Müller,[8] who in 1884 reported his work on nitrogen metabolism in typhoid fever. Subsequently, cancer, erysipelas, pneumonia, and tuberculosis were studied by, respectively, Müller,[9] Riethus,[10] Von Leyden and Klemperer,[11] and Ott.[12] From these studies came the term "toxic destruction of proteins." That fever *per se* does not cause this "toxic" destruction was shown by Graham and Poulton.[13] This first spurt of interest in protein also included the study of the protein needs of pregnant and nursing women,[14,15] while in pediatrics, as early as 1905, Rubner and Heubner[16] reported on the protein metabolism of the growing child.

The prevalence of famine in various parts of Europe during World War I gave impetus to observations by many workers on the effects of starvation, including the relationship between the level of blood proteins and edema.[17a,b]

In the interval between the two wars, some studies on various aspects of proteinology continued, with the development of new techniques and the perfection of old ones. New and important concepts were also formulated. Among these may be mentioned the studies of Van Slyke *et al.*[18] on amino acids, of Whipple *et al.*[19] on blood proteins and hemoglobin formation, and their concept of the dynamic state of body constituents, later to be confirmed by Schoenheimer[20] by the use of isotopes. Important techniques for determination of the fluid compartments of the body, of the circulation time, electrophoresis, a roentgenologic method for the determination of heart size, new psychologic tests, and a better comprehension of endocrinology, particularly of the adrenal cortex, were developed. Cuthbertson's findings[21] of increased azoturia following fractures extended the concept of

From the Creedmoor Institute for Psychobiologic Studies.

"toxic destruction of proteins" to the field of traumatology, and the studies of Ravdin and his group[22] on the relation between wound dehiscence and hypoproteinemia awakened clinical interest in protein involvement in disease. Meanwhile, the more general writings of McLester[23] and of Youmans[24] laid the foundation for a better appreciation of the role of nutrition in disease.

World War II gave a new impetus to protein and other nutritional studies. Ancel Keys' Minnesota project,[25] which may be considered as an up-to-date, "streamlined" counterpart of the project of Benedict and his colleagues of the Carnegie Laboratory of Nutrition,[26] collected an encyclopedic mass of knowledge and clarified a large area of the phenomenology of starvation. The observations of Walters *et al.*[27] on Japanese-held Indian prisoners of war, of the starvation team in Holland,[28] and of Mollison[29] on the inmates of the Belsen concentration camp, supplemented and extended the observations of the Minnesota investigators.

Historical Development of the Present Trend

Surgery

The dormant state following the first spurt of work on "toxic destruction of proteins" in clinical conditions may have been partly due to the fact that there was little therapeutic application of what was learned from these previous studies. The revival of interest in clinical proteinology may be attributed to the dramatic results of the application of high protein intake in surgical conditions. In relatively rapid succession came the introduction of the intravenous use of protein hydrolysates by Shohl *et al.*,[30] subsequently carried forward by Elman *et al.*[31] into surgical conditions, and the series of reports by Co Tui and his group on protein loss and the effect of hyperproteinization in decubitus ulcers,[32] in gastric surgery,[33,34] and in burns.

Of interest to clinical proteinology are the findings of the Co Tui group,[33–40] subsequently supported by the reports of other workers, that: (1) proteins are essential to the maintenance of tissue integrity; (2) the level of protein intake for the hypoproteinic patient may have to be as high as 250–500 Gm. daily—that is, the optimum level for replenishment approximates or even exceeds that for optimum growth; (3) the hypoproteinic subject is able to deposit nitrogen far in excess of what contemporary writers have thought possible; (4) the large deposition of nitrogen is associated with acceleration of rehabilitation and convalescence; (5) the catabolic or antianabolic period following injury can be eliminated by increasing the level of intake.

These points furnish the major scaffolding on which clinical proteinology is being built.

Internal Medicine

Although the work on "toxic destruction of proteins" was done on medical conditions, and although Albright's[41] monumental work on Cushing's disease and Farr's [42] study of nephrosis gave medical proteinology a good start, it cannot yet be said that the protein factor in general medical conditions is fully appreciated.

The efficacy of protein hydrolysate in the treatment of peptic ulcers, reported first by Co Tui *et al.*, [43,44] has been subsequently confirmed by several workers, among them Kenamore,[45] Smith,[46] and others. The response to the hydrolysate regimen may be divided into two parts: (a) symptomatic relief; (b) healing of the ulcer. The protein hydrolysates appear to be effective in both. Their antacid property is weak, and it is not likely that it plays a dominant role in symptomatic relief. The finding[47] of immediate relief of pyloric obstructions by the oral administration of protein hydrolysates, of changes in the motility of the gut,[48] of reduction in both hydrochloric acid and pepsin secretion,[49] and of a "protective action" exerted by protein hydrolysate on the gastric mucosa[50] suggest that other effects of hyperaminoacidemia may play a role.

Many ulcer patients suffer from hypoproteinia, although this deficiency is rarely reflected in the plasma protein level. Heretofore, this hypoproteinia has been attributed to a reduction in intake resulting from dis-

tress, or to the neglect of the nutritional factor in the preoccupation with the antacid factor. However, the observations of Gray[51] on chronic stress in peptic ulcer indicates that the oversecretion of protein catabolic agents in "chronic stress" may play a role in causing hypoproteinia in this disease.

Hypoproteinia retards wound healing, and it is in the correction of this deficiency by inducing acceleration of wound healing that protein hydrolysate plays its nutritional role.

The results reported by Boines[52] on the application of hyperproteinization in poliomyelitis, and by Ravdin, *et al.*,[53] Vars and Gurd,[54] and Morrison,[55] in liver disease, the work on the effect of adequate protein intake on corticotropin (ACTH) production[56,57] and the role in turn of corticotropin on the renal excretion of a pressor substance,[58-61] linking protein metabolism through endocrinology with hypertension, augur a brilliant future in this field.

Pediatrics

Although earlier work centered mostly on growth, the effects of disease on protein nutriture and vice versa have not received attention until recently. Yet it was actually in pediatrics that protein hydrolysate was first used. Recently Miranda[62] and Lynch[63] have called attention to "hypoproteinosis" in children and to the necessity for its correction by an adequate diet.

Terminology

The author[40] has proposed the term *hypoproteinia* for the systemic deficiency of protein in the body, as differentiated from *hypoproteinemia*, denoting deficiency of blood proteins. The term *hypoproteinia* is analogous to *hypoxia* for deficiency of systemic oxygen, of which *anoxemia*, deficiency of blood oxygen, was the forerunner. The term *normoproteinia* has accordingly been proposed for a normal state of body proteins, although *euproteinia* would perhaps be just as acceptable.

The hypoproteinia caused by starvation may be called *primary hypoproteinia*, while that following disease and injury may be termed *conditioned hypoproteinia*. However, in accepting these modifiers, it must be remembered that hypoproteinia does not present as pure a picture as the deficiencies caused by the loss of specific nutrients. On the one hand, in starvation, the hypoproteinia is due not only to the inadequacy of protein intake, but also to insufficient caloric intake; body proteins are destroyed to supply the organism's caloric needs. This obligatory destruction of body proteins imposed by caloric needs becomes a "conditioning" factor. On the other hand, neither does the hypoproteinia following disease present a pure picture, since there is almost always the factor of insufficient intake of both proteins and calories.

The Importance of Protein to the Body

The importance of protein in the body derives from the facts that (a) it is, next to water, the most abundant body constituent; (b) it forms the matrix of the cells, cytoplasm as well as nucleus; (c) it is inextricably involved in the maintenance of the integrity of the fluid compartments of the body as well as its tissues; (d) it plays an important role in immunological processes; and (e) it enters into the composition of the enzymes without which life is impossible.

These statements are only a more detailed itemization of the statements made years ago by Mulder[1] and by Verworn.[64]

Altered Protein Metabolism in Disease and Injury

In disease and injury, protein metabolism may be adversely affected in several ways. First, the reduced appetite associated with disease almost always reduces both caloric and protein intake. This would tend to induce the body to burn up its carbohydrate, fat, and protein stores, which, if of insufficient magnitude, would alone cause primary hypoproteinia. Early ambulation has contributed to the mitigation of this factor by restoring appetite earlier.

Second, in gastrointestinal conditions, digestion and absorption may be affected adversely, and discharge from fistulas, or diarrhea, may side-track the alimentary stream or prevent absorption.

Third, large losses of nitrogen from the body could occur through the loss of biological fluids, drainage, blood loss and body exudates. We have shown, for instance, that in burns, over 19 Gm. a day of nitrogen can be lost in the exudates from the burned area.[35] The seepage of cerebrospinal fluid, or of the discharge from a profusely draining sinus, could likewise cause considerable protein loss.

Fourth, immobilization and bed rest cause nitrogen loss, which has been interpreted by Cuthbertson[65] and by Deitrick *et al.*[66] as being due to the atrophy of disuse. This also is minimized by early ambulation.

Fifth, the "toxic destruction of protein," as expressed by the increased nitrogen excretion of the catabolic period, is more pronounced in the normoproteinic than in the hypoproteinic. Albright[41] and Browne *et al.*[67] have related this to Selye's "alarm reaction."[68,69] The azoturia may reach a level of over 20 Gm. of nitrogen a day. This phenomenon has been linked to the heightened secretion of the glucocorticoid hormones from the adrenal cortex, presumably either cortisone or hydrocortisone, both protein catabolic agents. This effect has been studied by Browne,[67] Howard,[70] Grossman *et al.*,[71] and recently by Moore.[72] This reaction is thought to be irreversible, because such high daily intakes of nitrogen as 20 Gm. (135 Gm. protein) do not reverse the nitrogen balance. Food proteins given during this "catabolic period," or period of "obligatory protein rejection" (formerly thought to last weeks, but now a few days) are presumably burned and eliminated. The teleological explanation for this was thought to be an effort of the organism to mobilize amino acids from its own tissues for the purpose of repair. According to the irreversibility theory, during this "natural" period of "obligatory protein rejection," the body not only must destroy some of its own tissues, but the mechanism mobilized for this purpose is so indiscriminate that this destruction cannot be prevented even if amino acids are made available from outside sources.

We have shown[37] that destruction of protein is reversible not only in cases of cholecystectomy and gastrectomy, where a possibly preëxisting hypoproteinia may facilitate reversibility, but also in herniotomy and appendectomy. In the herniotomy cases, the patients were normal except for a structural defect, while in the appendectomy cases an acute local inflammation in a hitherto normal person would be expected to worsen the catabolic response. Co Tui, on the basis of work on oral amigen,[37,38] a product of fairly uniform composition, has postulated a specific range of nitrogen intake for each disease.

TABLE I
Critical Ranges of Nitrogen Intake in Surgical Conditions

Surgical condition	Nitrogen intake	Cases studied
	Gm./KBW	
Gastrectomy	0.27 –0.42	25
Cholecystectomy	0.224–0.339	9
Herniotomy	0.147–0.182	18
Appendectomy	0.184–0.359	7

Table I shows these levels. This postulate would, of course, not be verifiable with native proteins with their heterogenous composition, but should be verifiable with pure amino acids as used by Rose.[73]

The example of intakes of as high as 20 Gm. of nitrogen resulting in precarious positive balances has been cited as supporting the irreversibility thesis. A moment's reflection will show the weakness of this argument. It is conceivable that, in a specific disease, a larger amount of one or more specific amino acids is required than is furnished by the proteins represented in the 20 Gm. of nitrogen. In that case, a positive balance would not be possible.

Starr *et al.*[74] showed that patients in positive balance during a limited experimental period manifested, on the average, greater efficiency and showed fewer abnormal complexes in the ballistocardiograph, than those who had been in negative balance.

Werner and associates[75] have confirmed Co Tui's findings in cases of gastrectomy and fractures of long bones. While the Werner group[76] is inclined to doubt the presence of an endocrine factor, the work to date on the secretion of corticotropin and cortisone in

stress leaves little doubt that these hormones play a significant role.

Support against the irreversibilty thesis is forthcoming from two other sources. Engel *et al.*[77-80] have shown in the fasted animal that the protein catabolic response to either adrenal cortical hormone or stress can be abolished by adequate administration of carbohydrates and amino acids. And Madden[81] gave a mixture of amino acids containing radioactive methionine intravenously to experimental animals with the acute injury of a turpentive abscess and found that under these conditions radioactive sulfur in comparable amounts appeared in the tissues both of the experimental animals and controls. As an editorial in a recent issue of the *J. A. M. A.*[82] expressed it: "There seems little or no support for the idea that amino acids after injury are useless in protein nutrition and that if given they merely act as a source of energy. . . . Food is an important requirement under most, if not all, conditions and protein seems no exception to this rule."

Phenomenology of Hypoproteinia

This has been dealt with extensively in the Minnesota project.[25] However, the data amassed in this project have, by the very nature of the work, their limitations. The voluntary experiment, however heroically designed, cannot be carried out to the point of endangering the subject, and, therefore, the hypoproteinia thus produced cannot be expected to reach the severe grades frequently encountered in actual starvation or in disease. Thus, the monumental data of the Minnesota project must be evaluated with the understanding that these phenomena occurred in the course of a hypoproteinia involving approximately a 25 per cent loss of body weight. Neither can the interplay between hypoproteinia and disease be observed under such experimental circumstances.

For knowledge of lower grades of hypoproteinia, we must rely upon observations made on cases of starvation, such as were made by Walters *et al.*[27] on Indian prisoners of war held by the Japanese, by Mollison[29] at the Belsen concentration camp, and by Burger, Drummond, and Sandstead[28] in Western Holland, or on the hypoproteinia produced in association with disease, as in cases reported by Clark *et al.*[83] and by Co Tui.[40] Chortis[84] has contributed valuable material on the interaction of hypoproteinia and pulmonary tuberculosis. However, the data obtained in both starvation and disease must all be qualified, either by environmental difficulties or by the effects of disease.

Loss of body substance is one of the cardinal findings in hypoproteinia. It is not known whether proteins are withdrawn from the body uniformly, leaving every protein-constituted cellular and chemical entity poorer in quality, or whether the number of cells and chemical entities is reduced, thereby preserving their quality. This perhaps depends upon the rapidity of protein withdrawal. In acute conditions, where the loss of protein is rapid, the deteriorated physiology of the organism perhaps reflects the deterioration of the entire protein structure. But where the organism has had time to "readjust," it is probable that the size of the organism is reduced in order to conserve the quality (protein-content). The validity of this thesis remains for further study.

One of the important manifestations of the loss of body substance is, of course, loss of weight. This loss is usually partially masked by storage of water, which according to Denz[85] is increased on activity and eliminated at bed rest. With the ambulant patient, this increase in water storage is expressed in increased plasma volume and thiocyanate space, but at bed rest, the plasma volume is decreased, so that a hypovolemia is usually found. It is this lability of the water metabolism which explains the difference between the findings on patients of Clark *et al.*,[83] on the one hand, and, on the other, of Keys[25] and Mollison[29] on starvation victims, and of ourselves on patients. The plasma volume, therefore, according to the T-1824 method of Gregerson,[86] is elevated in the active patient but may be decreased at bed rest.

If the volume of extracellular fluid is measured by the sodium thiocyanate method,[87] it is usually found to be greater in the active

patient. The rise may be more virtual than real, since in hypoproteinia there is usually an increase of cell permeability, allowing some of the dye to enter the cells—thereby giving a greater dilution and, therefore, a higher reading. It would be well to check this method of determination with others now available, such as mannitose or the inulin space. We have determined the total body fluid[88] using heavy water, and it does not seem to be significantly changed.

Upon reversing the nitrogen balance from negative to positive, there is sometimes such a large diminution of body water that there may be an initial loss of weight.

In hypoproteinia, body shrinkage is accompanied by a shrinkage of body girth, of the size of the heart and liver, and, according to our observations, by a thinning of the venous walls, which, in conjunction with a low venous pressure, makes blood drawing difficult. There is a macrocytic anemia, but strangely enough not necessarily a reduction of either the albumin or the total plasma proteins, at least within the 25 per cent loss of body weight, as shown in the Minnesota project.

This maintenance of the level of blood plasma proteins perhaps indicates a homeostatic mechanism for preserving the important function of blood osmotic pressure upon which the blood volume depends. The first moiety to be decreased is the albumin, but the total plasma protein level is maintained by the increase in the alpha globulins. There is a low hemoglobin, although the anemia may be either normochromic or hyperchromic.

According to Cannon[89] there is a lowering of resistance to infection, and Wohl and his group[90] found a diminished ability to manufacture antibodies.

A low basal metabolism is the rule, associated with fear of cold, and disinclination to effort. A loss of sexual desire is associated with reduction of the sperm count. Skin turgor is decreased, and the skin assumes a "cachectic" look—sallow, water-logged, dry, and scaly. The hair, according to our observations, is much more easily detached than hair in normal persons or than the patient's own hair after rehabilitation. In association with the shrinkage of the heart, there is bradycardia and a low blood pressure. The liver shrinkage may be associated with fibrotic changes and damage to liver function. There is a low tonus of the abdominal viscera with slow emptying time.

Wounds do not heal well, but at what stage of hypoproteinia this impairment of wound healing occurs is at present not clear. At some stage, the tissues are unable to maintain their integrity, and pressure points break down into bedsores.[32] Where there is a preëxisting open wound, the granulation tissue is pale and boggy, and the surface of the wound itself dirty with a greyish exudate.

While the special senses (other than pain) do not seem appreciably affected at a body reduction of 25 per cent, in patients with greater loss there may be mental confusion, leading to what has been assumed to be incontinence. The sense of pain appears to be blunted.

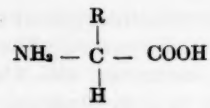
Diagnosis

The diagnosis at present must depend upon the loss of weight elicited in the history, and a detailed history would bring out the low efficiency, the disinclination to work and other symptoms discussed under phenomenology. A physical examination would disclose sallowness of the complexion, looseness of skin, poor tissue turgor, underweight, and in more pronounced cases the cachectic look. Laboratory findings mentioned above would support the diagnosis.

Basic Aspects

Chemical

Proteins are constructed from amino acids, which are also the source of such important nonprotein substances as creatinine, the purine bodies, and some hormones. The amino acids are, in turn, formed from the elements carbon, hydrogen, oxygen, and nitrogen. It is the distinctive presence of nitrogen which makes it possible to use the quantity of this element as an index of the quantity of protein. The amino acids may be represented by the model formula:



in which R represents a variable group, while the rest is a group common to all amino acids. The NH_2 group gives the *amino* part of the name; the COOH the acid part, while the distinctive character of the R group determines the individuality of each amino acid. It is in the R group that sulfur is found in the sulfur-containing amino acids.

By the linkage of the NH_2 group of one amino acid with the COOH group of another (peptide linkage), with the elimination of one molecule of water, a peptide is formed. Such linkages are pyramided until the protein molecule is achieved.

In the digestion or hydrolysis of proteins back into amino acids, the reverse process takes place. Since there are some twenty-one amino acids, the number of their possible combinations and permutations staggers the imagination. Thus, according to Abderhalden,[91] if the twenty amino acids commonly obtained in the hydrolysis of proteins are combined into peptides, in such a way that each occurs only once in the chain, almost two and a half quintillion (2,432,902,008,176,640,000) possible isomers of this peptide would be formed. And all would have the same percentage composition, would yield the same amino acids on hydrolysis, and would differ only slightly in their properties.

In both the anabolism and catabolism of amino acids and proteins, enzymes play a role, but we have only begun to learn which enzymes are involved, and their mode of action. Of hormones directly involved in protein metabolism, we only know of pituitary somatrophine and the glucocorticoids.

Metabolic

Classical physiology has taught the processes by which the proteins are prepared in the intestinal tract for absorption. The products of digestion or what may be called natural hydrolysates are absorbed in the digestive tract, enter the portal vein and are carried to the liver. From that point on, only the main outlines of the process are known, and those dimly and sketchily. Cannon *et al.*[92] have shown in the rat that the essential amino acids must be given simultaneously to be of use to the body. Whether the amino acids are distributed to the various tissues as amino acids, peptides, or simple proteins is not known, although Oncley[93] has shown that the lipoproteins provide one way of transfer.

In the normoproteinic individual, excess proteins are broken down and eliminated. How the body regulates its protein mass is also still unknown. Is it a matter of balance between the catabolic and anabolic hormones?

When proteins are catabolized, the resulting amino acids are, after deamination, degraded—partly through the same pathway as are carbohydrates and fats. Some of the degradation products can then be resynthesized into glycogen or fat. The amino part that is split off (deamination) appears in the urine principally as urea, or as ammonia. Some nitrogen from specialized substances forms creatinine, creatine, and uric acid. When used for energy, each gram of protein yields 4.1 calories.

Caloric Adequacy

It is to be remembered that energy requirements are of high priority in the physiology of the body. When not supplied with enough calories to meet this need, the body will burn not only exogenous proteins, but also the proteins in body tissues. The caloric needs are arrived at by multiplying the number of kilograms of body weight by the per Kg. caloric need. Riegel and his group[94] believe, on the basis of experimental work, that at least 30 calories per Kg. must be given in the form of carbohydrates. Rose, in his experiments on the amino acid requirements of man, has found that at least 45 calories are required.[73] In our own experience on severely hypoproteinic patients, we have used with satisfactory, if not necessarily optimum, results an overall amount of 50 calories per Kg.

Protein Requirements

The average protein requirement of the body had been set by Voit at 100–110 Gm. per

day, or, dividing by the factor of 6.25 to obtain the equivalent amount of nitrogen, 16–17.6 Gm. of nitrogen. This level prevailed until Chittenden's work, which reduced it to the level of from 6.7 to 8.96 Gm. of nitrogen per day. Flint[95] had this to say of Chittenden's work: "I have read this book through. It contains much valuable material. . . but the conclusions and suggestions as to the best diet for man are extravagant, impracticable and in the rigid application of doubtful value, if not dangerous."

The adequacy of the Chittenden level of protein intake may now be checked against the fundamental work of Rose on the tentative minima of the eight amino acids required for maintenance of nitrogen equilibrium. Table II shows these figures. The total nitrogen intake according to this work lies between 6.7 to 10 Gm. per person per day.

TABLE II

Minimum and Recommended Intakes for Normal Man When Diet Furnishes Sufficient Nitrogen for Synthesis of Non-essential Amino Acids
(Strictly Tentative Values)

Amino acid	Minimum daily requirement	Recommended daily intake	Subjects tested
	Gm.	*Gm.*	*No.*
l-Tryptophan	0.25	0.5	31*
l-Phenylalanine	1.10	2.2	22
l-Lysine	0.80	1.6	27
l-Threonine	0.50	1.0	19
l-Valine	0.80	1.6	23
l-Methionine	1.10	2.2	13
l-Leucine	1.10	2.2	8
l-Isoleucine	0.70	1.4	8

* All of these subjects have been kept in balance on 0.3 Gm. or less.

The recommended dietary requirements of the National Research Council[96] of 1 Gm. of protein per Kg. body weight a day, or 11.2 Gm. of nitrogen for a 70 Kg. man, is a compromise between Chittenden's and Voit's figures. Such a level, which is some 10 to 67 per cent above Rose's figures, may or may not always be adequate for the normal subject. But how this level came to be transferred to the diet of the ill and convalescent without experimental demonstration of its adequacy is still a mystery.

Nitrogen Equilibrium

One of the most frequent misconceptions is that of the significance of nitrogen equilibrium. The attainment of this equilibrium has been interpreted by some authors as signifying normoproteinia, i.e., a normal protein status; and the minimum of protein requirements for nitrogen balance has been equated with the protein requirements of the body. This identification may be justified in the normal individual, where only maintenance is required, but becomes pernicious when applied to the ill. As the body is deprived of adequate protein intake, its protein and caloric needs are correspondingly reduced—as reflected in decreasing azoturia. This has been shown in the professional starvers Levanzin[97] and Succi,[98] and recently confirmed in the dog by Allison.[99] With each day's loss of proteins from the body and further reduction of tissue mass, a lower and lower protein and caloric intake is required to attain equilibrium, so that nitrogen balance reached at such a low plane is more an indication of hypoproteinia than of normoproteinia. In fact, the ease of attaining equilibrium has been suggested as a means of detecting hypoproteinia.[100]

How this misconception may affect clinical practice is illustrated in the shift of attitude in the dietetic regimen in pulmonary tuberculosis. Some three decades ago, a rich diet of eggs, milk, and meats, i.e., a high protein diet, was advised as an important therapeutic measure in this disease. However, in 1926, there appeared a report[101] showing that it took no higher protein intake to achieve nitrogen equilibrium in cases of tuberculosis than in normal persons. This has been interpreted to mean that the protein needs of the tuberculous were no higher than those of the normal person, and an intake of 90 Gm. of proteins a day was recommended, with the warning that a higher intake might prove deleterious by provoking increased respiratory activity (because of the specific dynamic action of proteins).

Accordingly, in the most recent authoritative texts on tuberculosis, rich protein feeding is scarcely mentioned, while the possible dele-

terious effect of increased specific dynamic action has been stressed.[102,103] While it is true that the maintenance of good protein nutriture is not the only therapeutic measure in tuberculosis, the seriousness of the neglect of this factor, to which such an unbalanced attitude could lead, is well attested by the findings of Chortis[84] concerning the much more rapidly fatal outcome of hypoproteinic tuberculous patients.

Nitrogen equilibrium is only a method of biological bookkeeping and its value is at best circumstantial. Small balances either way are not significant, since the margin of error is high. Accordingly, slow small losses of protein may not be detectable by this method. Potassium balance has been used as a check on nitrogen balance and so also has weight, but both are subject to several sources of error. Perhaps a better check might be the total body solids as determined by subtracting the total body fluids from the body weight.[88] The gain in total body solids would, however, represent not only protein gains, but corresponding gains in minerals.

Grading Hypoproteinia

The matter of grading the stage of hypoproteinia is still unsatisfactory, now that hypoproteinemia has proved unreliable. Co Tui[40] has suggested calibrating the fluid lability as an index, since in his analysis of the parameters so far determined in hypoproteinic patients, he has found the changes in the plasma volume and the thiocyanate space to parallel the degree of hypoproteinia more than any other parameter. The level of nitrogen retention on a fixed level of intake has been used by Allison,[99,100] but this obviously cannot be done pretherapeutically.

The data of the Minnesota group[25] suggest that the creatinine coefficient, i.e., the ratio in milligrams of creatinine in 24-hour urine to body weight in kilograms, might be calibrated to serve the purpose of an index. The finding that the creatinine excretion fell faster than the body weight could be explained on the basis of storage of water. This method has the advantage of simplicity.

An ideal method would be one that would not reach a plateau too soon and would parallel faithfully the loss of nitrogen to the body. The development of such a method would be worth a great deal of research effort, since it would provide a frame of reference for the numerous phenomena connected with this deficiency.

Maintenance of an Adequate Protein State

Prevention of Hypoprotsinia in the Course of Injury and Disease

When a normoproteinic patient undergoes a simple surgical operation—herniotomy, appendectomy, cholecystectomy, or even gastrectomy—uneventful recovery usually ensues. According to Salzstein and Linkner,[104] complications following operations have been reduced with the institution of measurement and replacement of blood loss (a form of protein loss and replacement). Early ambulation has also shortened convalescence significantly. The feasibility of maintaining a positive N balance or at least of the mitigation of nitrogen loss throughout the entire postoperative period has been shown by Co Tui,[35] by Rhoads,[105] and by Elman *et al.*[31] But feasibility does not necessarily mean practicability. Whether the advantages gained by a postoperative period of no nitrogen loss are counterbalanced by the additional trouble incurred on the part of the staff and the patient has to be determined for each individual case. If it is shown that a normal protein status must be maintained throughout the entire postoperative period, intravenous feeding of carbohydrates and protein hydrolysates should be instituted during that period when oral feeding is not tolerated.

Moore[72] has used intravenous infusions of human albumin, on the principle that when the catabolic period is over, there will be available in the system some proteins that can be immediately anabolized. Oral feeding should be instituted as soon as appetite returns, and proteins—as large an amount as possible—in easily assimilable form must be given. Adequate caloric intake must be secured, preferably in the form of simpler polysaccharides such as dextrin and maltose.

In patients having surgical and medical conditions complicated by discharge of some

effusion, the problem of protein replacement becomes a more exacting one, and the techniques which have been worked out by the various workers who have studied this problem may all have to be employed (Co Tui,[33-35,40] Elman,[31] Rhoads,[105] Varco *et al.*,[106] and Werner *et al.*[107] The nutritional management of burns will not be dealt with here, since Blocker,[108] building upon earlier studies[34,109] has developed special and adequate techniques.

No severely hypoproteinic subject should undergo elective surgery. In the preparation of such patients Varco[106] has recommended that 7 to 10 days of dietetic rehabilitation be instituted for each 10 per cent loss of body weight, employing if possible 3 liters daily of a mixture containing a total of 240 Gm. of protein. If, however, emergency surgery must be performed, or if trauma is inflicted or disease contracted, the care of the protein status becomes a still more urgent matter.

In the rehabilitation of the severely hypoproteinic, it is necessary to get away from the strait jacket of the National Research Council recommended level of protein intake.[96] The aim is to give as large a quantity as possible of easily absorbable and high quality proteins and calories, and to give them as soon as possible. At this stage, the use of inadequate proteins, such as gelatin, is a mistake, since it takes up a part of the precious gastric space which should be used for superior nutrients. The response to the so-called "high protein diet" of 120 Gm. of protein daily is slow. As shown in Keys' Minnesota project,[25] even on an intake of 130 Gm. daily the rehabilitation was a slow process, showing none of the rapid gain in weight, strength and morale of the cases reported by Burger, Drummond, and Sandstead[28] and by Co Tui[40] with protein intakes of 3 to 4 times that level.*

Such levels are now being administered by Levinson and by Blocker in severe cases of burns, and recommended by Pollack and Halpern[110] in the severely hypoproteinic. This level approximates and even exceeds the optimum level for growth in children as found by Holt *et al.*,[111] Daniels *et al.*,[112] and Hawks *et al.*[113]

In patients for whom even the effort of swallowing is a strain, the food should be prepared in drinkable form. Feedings should be given as frequently as the patient can be prevailed upon to take them—every hour, or at least every two hours. Tube feeding may be necessary. Blocker has in fact developed a pump which keeps a constant stream of nutrients supplied to the gastrointestinal tract, making it possible to administer amounts of protein as high as 500 Gm. daily—a method of feeding which may be of great importance in convalescent care.

After the first 24 to 48 hours of hyperproteinization, there is usually a dramatic change, as has been reported above. This change consists of a brightening of mood, a return of strength, less fear of cold, greater inclination to effort, and a return of appetite. Burger, Drummond, and Sandstead's[28] description of this dramatic change may be quoted: "Recovery from a depressed and apathetic state, oedema and adynamia disappearing and they could be mobilized more quickly." There may be an initial loss of weight, a phenomenon explicable on the basis that the loss of body fluids is faster than the gain in tissue proteins. Where indolent wounds are present, the pale, edematous, poorly vascularized and soft granulation tissue is replaced by firm, better vascularized pink granulations. X-ray studies of the gastrointestinal tract may reveal that a preëxisting hypotonia and hypomotility have disappeared.

After the first 3 or 4 days of this acute stage, one may switch to kitchen-prepared food, cooked for easy digestion. Even at this stage, gastric capacity is still too precious to waste on foods of large roughage, or on such inadequate proteins as gelatin. The kitchen-prepared food is used as a scaffolding for the overall dietetic program and as a token of the patient's return to normal, but in fact most of the protein intake must still be supplied by supplementary feeding with native proteins, preferably in minute particle form, such as are found in "strained beef" or in milk proteins.

* In famine relief this level of intake may not prove practicable.

The use of hyperproteinization for the correction of hypoproteinia, while empirically successful, is from the standpoint of theory a gross and one-sided approach. In weaving the complex fabric of human tissues, many substances other than proteins participate: water, electrolytes, enzymes, vitamins, and hormones. What we are doing in hyperproteinization, in effect, is to furnish the deficient system protein and caloric adequacy, depending on nature to supply the rest. If one of the enzymes or hormones, or other essential constituents concerned with anabolism should fail, that generous supply of proteins would likewise be wasted.

Protein Preparations

Milk Proteins

Various combinations of milk proteins alone or of milk and dried egg proteins have been used, particularly by Pollack.[110] Most protein preparations in the market are milk proteins, either of casein or of lactalbumin. They have the advantage of being inexpensive and can usually be tolerated. Sometimes a hydrolyzed protein is added to such a mixture.

Strained Beef

This comes in cans prepared for infant feeding, but is also useful in the feeding of convalescent adults. The amino acid curve in the blood after administration of an equal amount of strained beef or of milk protein has been found by Co Tui *et al.*[114] to reach a peak in about 45–60 minutes, nearer the hydrolysate curve than that of roast beef. It can be tolerated up to as high an amount as 16 cans per day, each can containing 100 Gm., and while it is more costly than milk and egg proteins, it can be used when patients tire of these latter protein preparations or are allergic to them.

Protein Hydrolysates

While the protein hydrolysates have no place in normal nutrition and only a small place in the rehabilitation of the average case of hypoproteinia, their use is sometimes lifesaving. They owe their value to the fact that they can usually be dissolved in small volume and "slipped" into the patient, either in a refrigerated solution, followed by a carbohydrate chaser, or in a gastric tube. While hydrolysates cannot be tolerated by some 50 per cent of patients, many do develop a tolerance for them when the dose is gradually increased, say from 100 Gm. on the first day. Some patients develop diarrhea, the diarrheal dose varying in different patients. In most cases the diarrhea can be controlled by such preparations as Kaopectate® or Kaomagma®, or by mixing them with a slightly hydrolyzed preparation which usually causes constipation (Lactenz®).

Intravenous Protein Preparations

There are many such preparations available, having different proportions of nitrogen and carbohydrates, and of different pH. The occurrence of thrombosis at the site of injection has been one deterrent to the more widespread use of intravenous alimentation. Pyrogenic solutions are rarely encountered nowadays, unless the time between opening a bottle and administration has been over 3 hours. Occasionally urticaria and rash have been encountered with intravenous as well as with oral preparations. The use of intravenous fat,[115] while promising, has not yet become practicable.

Summary and Conclusions

In this paper on the fundamentals of clinical proteinology, the following aspects have been dealt with:

(1) A brief history of its development from Mulder to its present status in the various specialties, and its potential developments in the future.

(2) Basic concepts in general proteinology underlying its clinical application, such as: importance of proteins to the body, the chemical aspects of protein formation, caloric and protein requirements and their interrelationship in the normal subject.

(3) Mechanism of protein loss in disease and injury.

(4) Hypoproteinia and its phenomenology, including symptomatology and diagnosis.

(5) Protein and calorigenic preparations available for clinical use.

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Resumen

Los fundamentos de la proteinología clínica

En este trabajo sobre los fundamentos de la proteinología clínica se consideran los siguientes aspectos:

(1) Un esbozo histórico de su desarrollo desde Mulder hasta su situación actual en las diversas especialidades y sus posibilidades futuras.

(2) Los conceptos básicos de la proteinología general que fundamentan su aplicación clínica, tales como: las importancia de las proteinas para el organismo; los aspectos químicos de la formación protéica; los requerimientos calóricos y protéicos y su interrelación en el sujeto normal.

(3) El mecanismo de la pérdida protéica en las enfermedades y en los traumatismos.

(4) La hipoproteinia y su fenomenología, incluyendo sintomatología y diagnóstico.

(5) Las preparaciones protéicas y colorigénicas disponibles para uso clínico.

Editorial

The Reluctance of Physicians to Admit That Chronic Disease May Be Due to Faulty Diet

A challenging problem for the nutritionist is the fact that physicians, who so often ascribe acute illness to a recent dietary mishap, have always hated to accept any theory ascribing chronic disease to bad food. Thus, the causation of scurvy was clearly and convincingly described by Bachstrom in 1743; lemon juice as a preventive and cure, with excellent resistance to storage, was recommended in Lind's treatise in 1754. A critical test was given by the British navy in 1795, the year of Lind's death, and the brilliant success led to the orders which abolished scurvy forever from British ships. Thanks to Lind's work, Nelson's sailors enjoyed unusual health during the decades when his "distant storm-tossed ships stood between Napoleon and the conquest of the world."

In 1908 Holst and Fröhlich found that the guinea pig, alone among domestic or laboratory animals, developed scurvy on diets like those of the sailors before 1800, and could be cured by lemon juice. This test animal later served to control the isolation and synthesis of ascorbic acid (vitamin C). But all this left the medical profession cold. For a decade after Holst's work, and a century and a quarter after the Lords of the Admiralty accepted Lind's theories, the *Encyclopedia Britannica* and leading medical texts disparaged the dietary theory and spoke favorably of "infection by an unknown microbe." In 1950 a text widely used by English-speaking students of medicine stated that "young men totally deprived of vitamin C, but leading an active life with outdoor exercise have not developed any symptoms or signs of scurvy over prolonged periods." Thus two centuries after Bachstrom's studies and twenty years after Szent-György identified the chemical nature of the missing substance in scorbutic diets a distinguished internist found the theory so distasteful that he allowed himself to forget that sailors who died of scurvy had been young men getting 12 to 20 hours daily of "active outdoor exercise" on the decks and in the rigging of their ships, and that lemon juice had promptly cured every symptom and sign.

The story of scurvy is now being reënacted in the history of atherosclerosis and the effect of excessive dietary cholesterol. Rupture of the left ventricle was first described by William Harvey in 1649, in the heart of a noble knight. By 1900 physicians recognized that coronary atherosclerosis and angina pectoris were "afflictions of the better classes, not of the working classes" (Osler). Indeed, atherosclerosis was never found in wild, domestic, or laboratory beasts, no matter how fat or how old they became. The lesions were far more severe in those people who regularly used eggs and milk products than in those who ate only cereals, vegetables, fruit, fish, and meat.

Windaus and his pupils found cholesterol abundant in the atherosclerotic plaques and in the diets of those who developed the lesions. They knew that all animals synthesized this substance, and that herbivors on cholesterol diets excreted large quantities of cholesterol in

bile and milk. The facts of comparative and of geographic pathology suggested to Anitschkow that dietary cholesterol might be the cause of atherosclerosis and in 1914 he reported that the rabbit, normally free of atheroma, developed severe lesions when fed cholesterol. His work was confirmed in Europe, and in America, where feeding cholesterol to chicks and hypothyroid dogs also was found to produce severe disease. No lesions occurred in control animals on similar regimes but receiving no cholesterol by mouth. In all three species, as in man, arterial hypertension accelerated the development of the lesions.

Antischkow made an inspired guess when he ignored endogenous cholesterol as a possible source of the lesions. In alloxan diabetes or following intravenous injections of detergents, such as Tween 80®, extremely high endogenous plasma cholesterol levels have been maintained in rabbits.[1] No atherosclerotic lesions developed, while controls with lower plasma cholesterol levels due to *fed* material showed widespread atherosclerosis. At the University of California, endogenous cholesterol was tagged by giving rabbits radioactive hydrogen as $H\,^{3}_{2}\,O$; in others the dietary cholesterol was tagged. This study[2] showed that "exogenous cholesterol forms the bulk of the cholesterol in atheromatous deposits found in cholesterol fed rabbits" although "cholesterol synthesis continues even in the face of massive prolonged cholesterol feeding."

No one has yet produced such lesions in mammals except by adding cholesterol to their diets, although innumerable attempts have been made by increasing endogenous production, by causing severe injury to arterial walls by direct trauma, by experimental hypertension with periarteritis, and by injuring arteries with diets low in choline, riboflavin, and other factors. Similarly, in man, atherosclerosis decreases in wartime with restriction of dietary cholesterol, although other dietary deficiencies, as well as work, worry, and the increase in the infectious diseases, would be expected to increase "degenerative" diseases during blockade or enemy occupation.

"It is a principle well established in medicine that agents harmful to laboratory animals must be assumed to be harmful to men until definitely proved otherwise" (Shields Warren). Most clinicians and science writers take an opposite view when discussing atherosclerosis. Their bias toward this problem is summed up in their usual statement: "The rabbit has no cholesterol in its normal diet and hence lacks ability to handle this substance." As a matter of fact, rabbits secrete milk twice as rich in cholesterol as human or bovine milk, and baby rabbits consume far more milk per kilo per day than human babies.[3] Cholesterolosis of the aorta is commonly found in human infants prior to weaning, and similar lesions develop in most suckling rabbits. After weaning, these plaques disappear quickly both from children and young rabbits. A final point of likeness between man and the rabbit is that a few individuals of both species show little rise in blood cholesterol and no atherosclerosis as a result of prolonged cholesterol excess in the diet. The mechanism of "resistance" is unknown. The percentage of "resistant" men, who show no evidence of coronary or aortic atherosclerosis by the age of 55, is less than 10 per cent according to necropsy findings reported from Minnesota.

It is now clear that endogenous cholesterol plays no part in atherosclerosis except when hens are kept under high estrogenic stimuli for periods much longer than the laying period of wild fowl, and perhaps in some human beings with hypercholesterolemia who continue to excrete abnormal amounts of cholesterol in the bile even on cholesterol-free diets. In most such cases, however, blood levels of cholesterol fall strikingly when the patient is placed on a low cholesterol diet, liberal in protein.

Since two centuries of practical and experimental study have failed to convince some physicians that diets of salt pork, beans, and flour may be inadequate for maintaining health, it probably will take a long time to convince the profession that diets rich in eggs, butter, and cream cause the disease which now kills nearly one out of every three physicians. The biologist knows that such diets are as alien to adult mammals as those which cause scurvy, beriberi, and pellagra.

The nutritionist may fail to correct this

type of abnormal diet, but industry will find it profitable to have those who use these foods add sitosterols or dihydrocholesterol[4] to the diet. These substances block cholesterol absorption, and prevent both hypercholesterolemia and atherosclerosis in the experimental animal.

Thus, by a slight increase in cost of his foods, man may learn to eat cholesterol and not absorb it.

—WILLIAM DOCK, M.D.

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Dietotherapy

DIETARY NOMENCLATURE

A UNIVERSAL, or at least widely accepted, system of dietary nomenclature is fundamental for the correct interpretation of the physician's orders, the unification of dietary regimens, the evaluation of new diets, and the comparison of results. The name of a diet should immediately convey to the physician, nurse, and dietitian a similar, if not always identical, description. The terminology should be commonly understood and accepted by the physician in a hospital in New York City, the nutritionist in the public health department of a city in Texas, or the dietitian in a food clinic in Los Angeles. Even the patient's acceptance of the diet may be conditioned by the name which is given to the diet.

Exact Nomenclature Determines Dietary Effectiveness

A primary requirement of good dietary nomenclature is exactness in describing the level of nutrients, when such quantitation is important to the final result. It would be unthinkable for a physician to prescribe a medication without indicating the amount to be used. Yet, the use of inexact terms such as "high" and "low" in describing diets is commonplace, and usually results in a great deal of confusion. As a rule, modifying terms are related to a standard for normal intake such as the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council.[1] For example, when a "high protein" diet is ordered it is customary in most hospitals to provide approximately 100 to 125 Gm. protein daily. This protein level is high when referred to the 70 Gm. protein allowance for a man in health. It is likewise a liberal diet for many ill persons. However, it would be the normal or expected protein intake for pregnant or lactating women, or it might be too low for satisfactory nutrition in certain surgical situations or in diseases of the liver. Thus, in many situations it would be necessary to specify more exactly the level of protein desired.

Similarly, a "low calorie" diet may succeed or fail depending upon the extent to which calories are restricted. The 800, 1200, and 1500 calorie diets are all "low calorie" when referred to normal requirements of the adult. If a physician fails to specify the caloric level which is desired for the patient, the dietitian or nurse will usually select a moderate level of restriction such as the 1200 calorie diet. Although such a diet can be planned to provide all of the nutritive essentials, it may entirely fail to produce the expected weight loss, or, on the other hand, may occasionally be too severe a program.

Exact Nomenclature Aids Dietary Evaluation

Progress in diet therapy is dependent upon a continual evaluation of the results obtained by various investigators. Such comparative studies are unquestionably facilitated by exactness in describing the level of a nutrient or of nutrients. At the present time considerable confusion still exists concerning the efficacy of diets restricted in sodium. Diets described as "low sodium," "low salt," and even "salt free" are known to vary from less than 200 mg. to more than 1000 mg., depending on individual planning. Thus, a description in general terms may mean that one investigator is basing his conclusions on the use of diets providing extremely limited amounts of sodium, while another investigator is basing his find-

ings on the use of much more liberal diets. Obviously, comparison of diets at such widely varying levels of intake is unreliable. Duplication of studies and considerable misinterpretation can be avoided when the physician, nurse, and dietitian are concerned with dietary planning at specified nutrient levels.

Nomenclature Depends on Knowledge of Food Values

Suitable dietary nomenclature is dependent on a knowledge of food values and on the behavior of foods in the body. To cite the currently popular low sodium diet again, the knowledge that almost all foods contain some naturally occurring sodium will emphasize the fact that no diet is, in a correct sense, "salt free." The term "low salt" is also insufficiently exact when sodium restriction is required, since many foods may be prepared without salt but may nevertheless contain important amounts of naturally occurring sodium or of added sodium products other than sodium chloride—such as baking powder, baking soda, and numerous others used in food processing.[2] The interchangeable use of the words "salt" and "sodium" in describing sodium restricted diets cannot be condoned. Indeed, one who uses terms such as "salt free" and "low salt" admits that he understands the diet poorly, or is careless in his use of terminology.

Adequate information on food values will eliminate certain nomenclature as well as lists of diets from daily usage, since it will be realized that some dietary modifications are impossible, or at least highly impractical. The so-called "high vitamin" or "high iron" diets do not in any sense provide therapeutically effective levels of most of the vitamins or of iron, respectively. Diets so described have no place in diet manuals and in textbooks.

Problems of Dietary Nomenclature

No group of diets suffers as much from undesirable practices in nomenclature and subsequent misinterpretation of orders as do the regimens for diseases of the gastrointestinal tract. Unfortunately, there is little information on the behavior of certain foods in the gastrointestinal tract. This is especially true with reference to so-called "low residue" diets. There appears to be little discrimination between the use of the words "fiber" and residue." It has been noted that some sources reduce the amount of fiber only, thus permitting pureed cooked fruits, vegetables, ground or tender meats, milk, fine cereals, bread, etc. Other regimens omit milk, fruit, and vegetables. Until reliable information is available, one cannot hope to achieve unanimity in the description of such diets; obviously, the term "low residue" will continue to mean widely divergent diets to different people.

Nomenclature Should Avoid Disease Names

All too frequently diets are named for disease conditions. For example, a patient is told that he requires an "initial ulcer diet," an "ambulatory ulcer diet," or an "ulcer discharge diet," and is given an instruction sheet so headed. Why should the patient need to be reminded of the fact that he has ulcers every time he consults his diet sheet? What is the meaning to the patient of the words "initial," "ambulatory," and "discharge"? Isn't this merely an example of carelessly adopted jargon by the professional person? Surely one could find a more appropriate name for the diet, such as "bland diet," "high protein bland diet with six meals," etc. Many diet manuals now designate the progressive dietary program used for peptic ulcers as Bland Diet I, II, III, etc.

Numerous examples of diets named for symptoms of diseases could be mentioned: "gastrointestinal section diet" (bland diet); "gallbladder diet" (moderate or low fat diet); "anticonstipation diet" (high fiber diet); "cardiac diet" (soft 500 mg. sodium diet); "colitis diet" (bland high protein diet); "nephrosis diet" (high protein 800 mg. sodium diet); yes, even "antivomiting diet" (dry diet)! Not only is the psychologic connotation of such nomenclature unfortunate, but the use of a disease name suggests that a diet is limited to that condition alone. Thus arises an unnecessary multiplicity of diets, usually varied in the slightest of details.

Nomenclature Should Avoid the Names of People

The use of a person's name for a diet is not desirable. True, some named diets such as the Sippy and Meulengracht diets have become so well known as to convey a definite description to anyone at all versed in dietary procedure. Even so, the "modified Sippy diet" means to some a liberal program graduated over a period of one week, and to others a severely limited, nutritionally inadequate progression over a three to four week period. More frequently, a dietitian, nurse, or physician has no knowledge of a diet by a person's name and may be at a total loss to duplicate a regimen.

Characteristics of Good Dietary Nomenclature

The Diet Therapy Section of the American Dietetic Association has recognized the need for a clarification of the terms used in dietetics and in describing diets. The newly revised *Handbook of Diet Therapy*[3] includes a glossary prepared by this Section, as well as descriptions of the diets named in this glossary.

From the foregoing discussion it is apparent that the nomenclature for most diets can meet these requirements:

1. Terminology should be related to the modifications of the normal diet; that is, it should be stated as an increase or decrease in one or more nutrients, change in consistency, flavor, etc.

2. Dietary nomenclature should specify nutrient levels whenever quantitation is essential to the success of the diet. Thus, just as the amount of protein, fat, and carbohydrate is specified for the diabetic patient, so the sodium level will be stated for restricted sodium diets, the calorie level for low calorie diets, etc.

3. Reference to diseases or symptoms should be avoided in describing a diet.

4. Names of persons should not be used to designate a diet since underlying principles are usually not clear.—CORINNE H. ROBINSON

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AMERICAN BOARD OF NUTRITION

INCORPORATED

The American Board of Nutrition *announces that the following persons have been certified as* Specialists in Human Nutrition. *The certificants submitted applications prior to February 29, 1952, and were certified on the basis of training and experience in the field of human nutrition.*

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2. Adlersberg, David—New York
3. Albanese, Anthony August—St. Luke's Hospital, New York
4. Allen, Denver I.—U. S. Army
5. Alpert, Elmer—Merck and Co., Inc.
6. Anderson, Karl Richmond—The Rockefeller Foundation
7. Arnold, Aaron—Sterling-Winthrop Research Institute
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9. Bal, Mary E. R.—Columbia University
10. Basinski, Daniel H.—Children's Fund of Michigan
11. Bean, William Bennett—University Hospitals, State University of Iowa
12. Berryman, George Hugh—Abbott Laboratories
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24. Cartwright, George Eastman—University of Utah
25. Cayer, David—The Bowman Gray School of Medicine
26. Chow, Bacon Field—The Johns Hopkins University
27. Cowgill, George Raymond—Yale University
28. Cox, Warren Murdock, Jr.—Mead Johnson and Company
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30. DaCosta, Esther—Medical Nutrition Laboratory and Food and Container Institute, U. S. Army
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43. Gant, Ola K.—La Sierra College
44. Geiger, Ernest—Van Camp Sea Food Co.
45. Getz, Horace Raymond—The Charles Cook Hastings Home
46. Goldsmith, Grace A.—The Tulane University of Louisiana
47. Goodhart, Robert S.—The National Vitamin Foundation
48. Griffith, Wendell H.—University of California at Los Angeles
49. Harper, Harold A.—University of San Francisco
50. Harris, Philip L.—Distillation Products Industries
51. Hawley, Estelle E.—The University of Rochester
52. Hegsted, D. M.—Harvard University
53. Hillman, Robert Wright—New York State University College of Medicine at New York City
54. Hodson, Adrian Zachariah—Pet Milk Company
55. Horwitt, Max Kenneth—Elgin State Hospital
56. Hunscher, Helen A.—Western Reserve University
57. Ives, Margaret—American Can Company
58. Jackson, Sanford H.—University of Toronto, Toronto, Canada
59. Jolliffe, Norman—Department of Health, City of New York
60. Kark, Robert M.—College of Medicine, University of Illinois

61. King, C. G.—The Nutrition Foundation, Inc.
62. Koehn, Carl J.—Office of The Surgeon General, U. S. Army
63. Krehl, Willard Arthur—Yale University
64. Kruse, Harry Dayton—The New York Academy of Medicine, Inc.
65. Langwill, Katheryn Elizabeth—Drexel Institute of Technology
66. Leone, Nicholas Charles—National Institutes of Health
67. Levenson, Stanley M.—Medical College of Virginia
68. Levey, Stanley—University Hospitals of Cleveland
69. Lewis, George Truman—Emory University
70. Lewis, Robert Vickery—Providence
71. Light, Amos Ellis—The Wellcome Research Laboratories
72. Lowenberg, Miriam E.—Mayo Clinic
73. MacVicar, Robert—Oklahoma Agricultural and Mechanical College
74. Macy-Hoobler, Icie G.—Children's Fund of Michigan
75. Maynard, L. A.—Cornell University
76. McLester, James S.—Birmingham
77. Melnick, Daniel—The Best Foods, Inc.
78. Najjar, Victor A.—The Johns Hopkins Hospital
79. Odland, Lura Mae—Montana State College
80. Olson, Robert Eugene—The University of Pittsburgh
81. Oser, Bernard L.—Food Research Laboratories, Inc.
82. Parrott, Ernest M.—Medical Nutrition Laboratory and Food and Container Institute, U. S. Army
83. Peterman, Robert Adams—Merck and Co., Inc.
84. Pett, Lionel Bradley—Department of National Health and Welfare, Ottawa, Canada
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87. Pye, Orrea Florence—Columbia University
88. Robertson, Elizabeth Chant—University of Toronto, Toronto, Canada
89. Ryer, Robert, III—U. S. Army
90. Sarett, Herbert Paul—Mead Johnson and Company
91. Schilling, Robert Frederick—The University of Wisconsin
92. Schwimmer, David—New York
93. Scoular, Florence I.—North Texas State College
94. Scrimshaw, Nevin Stewart—Instituto de Nutrición de Centro América y Panamá, Guatemala City, Guatemala
95. Sebrell, William Henry—National Institutes of Health
96. Shank, Robert Ely—Washington University
97. Shils, Maurice Edward—Columbia University
98. Spector, Harry—Medical Nutrition Laboratory and Food and Container Institute, U. S. Army
99. Stare, Fredrick J.—Harvard University
100. Storvick, Clara A.—Oregon State College
101. Taylor, Clara Mae—Columbia University
102. Thompson, Ethel Marion—University of Arizona
103. Trulson, Martha Frederica—Harvard University
104. Voris, A. LeRoy—National Research Council
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107. Wetzel, Norman C.—Cleveland Heights
108. Wharton, Marion A.—The Ohio State University
109. Whitehead, Floy Eugenia—Harvard University
110. Williams, Ray David—Washington University
111. Wilson, James R.—American Medical Association
112. Youmans, John B.—Vanderbilt University
113. Young, Charlotte Marie—Cornell University

Since February 29, 1952, applicants are certified on the basis of training, experience and examination. The Board will meet in April 1953 to consider current applications. Applicants who are deemed eligible for examination will be notified of the date, place and procedure of the examination, after the meeting of the Board. Application forms may be obtained from the Secretary, Otto A. Bessey, School of Medicine, The University of Texas, Galveston, Texas.

Nutritional Quotes

Hemoglobin Biosynthesis

"The quantitative importance of amino acids in hemoglobin formation is illustrated by the amount of hemoglobin required for daily replacement. It is estimated that 8 Gm. of globin is destroyed daily by the average adult. This means, therefore, that approximately 14% of the total dietary protein intake of the average adult is required solely for the resynthesis of new hemoglobin. These data reëmphasize the importance of adequate protein, as well as iron, intake for the maintenance of a normal rate of hemoglobin synthesis in man."

—Editorial, *Journal of the American Medical Association* 150: 1223, 1952.

A Trace Mineral and Caries

"The findings of the present investigation indicate that there is a direct relationship between the degree of susceptibility to dental caries and the urinary selenium concentrations of the subjects.

"The results of our study suggest the possibility that the trace element selenium may render the teeth more susceptible to dental caries attack just as another trace element, fluorine, is known to provide a great deal of protection against dental caries."

—D. M. Hadjimarkos, C. A. Storvick, and L. F. Remmert. *Journal of Pediatrics* 40: 451, 1952.

Milk and the Older Person

"The one food most frequently neglected in diets of older women, usually because it is considered both fattening and expensive, is milk. The contribution of milk and milk products in nutrients and the relatively low caloric value per portion suggest a much wider use of this food by aging adults."

—M. A. Ohlson, L. Jackson, R. M. Beegle, D. Dunsing, and E. C. Brown. *Journal of the American Dietetic Association* 28: 1143, 1952.

Ambivalent Symptoms in Potassium Imbalance

". . . It should be noted that potassium excess with accompanying toxicity is also encountered, especially in renal failure, and that the symptoms and signs are indistinguishable from those of potassium deficiency. This danger, in relation to the administration of potassium for supposed potassium deficiency, is obvious, since either deficiency or excess may be fatal. Determination of the level of serum potassium is most helpful in this situation."

—J. B. Youmans. *Journal of the American Dietetic Association* 28: 1031, 1952.

Vitamins and Antibodies

"The available evidence would indicate that certain B vitamins, notably pyridoxine, pantothenic acid and pteroylglutamic acid, play a significant role in antibody synthesis."

—A. E. Axelrod. *Metabolism* 2: 1, 1953.

Diabetic Adaptation

"It may be profitable to look upon the diabetic not as an individual who is in constant danger of being harmed by the toxic effects of a high blood glucose level, but rather as an individual who is constantly protecting himself from the threat of a low blood glucose level by continually utilizing adaptive processes designed to conserve glucose and to diminish its utilization by the muscles. Such adaptive processes are classically appropriate to starvation, or to settings of stress which tend to cause a depression of the blood glucose. Their appearance in diabetic persons is consistent with what we know of their life histories, the setting in which their illness occurs and the symptoms associated with it."

—L. E. Hinkle, Jr., and S. Wolf. *Diabetes* 1: 383, 1953.

Free Diet in Diabetes

"Our experience with this group of diabetic children treated without dietary restrictions, and the comparisons made between this group and diet-treated series, have led us to the conclusion that the use of measured diets does not protect the patients against degenerative vascular complications to a greater extent than treatment with a free and normal diet, combined with adequate insulin therapy and regular supervision. Since, furthermore, a free diet offers diabetic children a chance to lead a happier, more natural and normal life, we consider it preferable to treatment with measured diets."

—Y. Larsson, A. Lichtenstein, and K. G. Ploman. *Diabetes*, 1: 449, 1953.

Hyperglycemia, Glycosuria, and Ketosis

"At the onset, it must be stated clearly that the main point is not whether hyperglycemia and glycosuria are in themselves harmful. They may well be injurious because of disturbances in fluid and electrolyte balances which they cause. However, the chief reason for directing attention to hyperglycemia and glycosuria is that they are convenient and reliable indicators of underlying metabolic abnormalities. They are way-stations on the road to ketosis. The clinician must decide whether he will set as his goal the mere avoidance of ketosis or whether he will attempt to approach the normal more closely by avoiding also hyperglycemia and glycosuria in so far as practicable."

—A. Marble: Editorial. *Diabetes* 1: 489, 1953.

Reviews of Recent Books

Nutrition and Diet in Health and Disease (sixth edition) by J. S. McLester and W. J. Darby, W. B. Saunders Co., Philadelphia, 1952, pp. 710, $10.00.

A book that goes through six editions obviously satisfies a definite need. The latest edition of this standard textbook on nutrition maintains the high level set by previous issues. Dr. Darby has joined the senior author in revising and rewriting large portions of the text. New material has been added and many references are from 1951–52. Several valuable tables enhance the practicality of the text. Thus, there are compilations of cholesterol, sodium, and potassium values of foods, list of available processed foods of low sodium content, etc.

Although the entire field of clinical nutrition is discussed, there is a somewhat disproportionate division of emphasis. Thus, the dietary aspects of atherosclerosis are covered essentially in two pages; nervous indigestion warrants four, including two of sample menus.

As with any textbook, certain statements may not result in universal agreement, such as: "He [the potential diabetic] should take sweets only in strictest moderation, preferably in the form of the simpler desserts and after meals—never as candy and similar sweets and never between meals. The avoidance of sauces is also advisable." The use of the ketogenic diet in the treatment of epilepsy is deplored, yet two pages are devoted to a detailed description and specimen ketogenic diets. The high calcium requirement of hyperthyroidism is not discussed.

Nevertheless, the book is remarkably complete, current, and authoritative. Its value is increased by chapters on satiety values of different foods, the question of roughage and digestibility, and the cost of food (which strangely enough appears under the heading of "Nutritional Factors of Lesser Importance").

The text reads well; the typography, format, and index are excellent. This book can be recommended as one of the basic texts in the field. S.W.

The Newer Knowledge of Hygiene in Diet by J. Sim Wallace, M.D., C.M., D.Sc., L.D.S., F.DS., R.C.S., F.A.C.D., Dental Items of Interest Pub. Co., Inc., Brooklyn, N. Y., pp. 264, $4.75.

This is more of a commemorative volume by one of the pioneers in dental physiology and pathology and nutritional study, than a text or reference on this subject. It is obviously written in support of, and in defense of, the author's thesis, that even under modern civilized conditions, dental caries can easily be prevented, or almost entirely prevented (without the use of fluorides).

Wallace places great importance on the diet, not only in respect to its nutritional aspect but also as it affects the teeth and alimentary tract before absorption, the latter being related to mouth hygiene. The beneficial effects of detergent diets are correctly stressed since fibrous foods aid in removing the adherent soft food debris from about the teeth. The sequence with which the different foods are consumed may be an important factor in the reduction of dental caries.

The chapters concerned with recent advances in dental caries control are grossly incomplete. The author, however, does correctly point out repeatedly that dental caries is not a deficiency disease and that what happens to the tooth after eruption is at least as important as what occurs during its formation.

This last publication, written by a once famous investigator in his late 70's, deserves a sympathetic reception. The book cannot, however, be generally recommended because of its poor organization, unnecessary and extensive quotations, and the general argumentive tenor of the presentation. L.W.B.

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Phosphorus Metabolism. Volume II, edited by William D. McElroy and H. Bentley Glass, The Johns Hopkins Press, Baltimore, 1952, pp. 929, $11.00.

Food in Health and Disease by Katharine Mitchell and Margaret C. Bernard, F. A. Davis Co., Philadelphia, 1953, pp. 688, $4.25.

Diseases of Metabolism (third edition), edited by Garfield G. Duncan, W. B. Saunders Co., Philadelphia, 1952, pp. 1179, $15.00.

The Chemistry and Technology of Food and Food Products (second edition), edited by Morris B. Jacobs, Interscience Publishers, New York, 1951, pp. 2580, 3 volumes: $12.00, $15.00, and $15.00.

Progress in the Chemistry of Fats and Other Lipids. Volume I, edited by R. J. Holman, W. O. Lundberg, and T. Malkin, Academic Press, Inc., New York, 1952, pp. 186, $7.00.

Familial Nonreaginic Food Allergy (third edition) by Arthur F. Coca, Charles C Thomas, Springfield. 1953, pp. 279, $10.50.

Abstracts of Current Literature

ABSTRACTERS

PEDIATRIC NUTRITION

The evaluation of the nutritional status of the infant and of the growing child presents certain difficulties. In infancy, the character and frequency of stools may be a significant factor in this assessment.

Stool Frequency of Normal Infants in First Week of Life. W. L. Nyhan. *Pediatrics* 10: 414, 1952.

The nutritional properties of a food for infants may be in part appraised by the effect it has on the feces of the infant. This paper provides valuable basic data on the stool frequency of normal infants in the first week of life. Observations were made on 800 infants on different types of artificial feeding regimens and breast feeding. The number of stools of the bottle-fed babies was statistically greater than in the case of the breast-fed babies. It is suggested that this difference may well be a simple reflection of the amount of food ingested, as the artificially fed baby was noted to receive more milk during the first few days of life than did the breast-fed baby. This simple consideration would be of great importance in appraising differences in the qualitative composition of foods in relation to stool frequency.—C. D. MAY

In the older child, as well as in the infant, the maintenance of normal height and weight curves is generally regarded as an important criterion in the evaluation of nutritional status. The effects of food shortages and poor environmental conditions are discussed in the following paper.

Growth Responses of the School Child to Changes in Diet and Environmental Factors. P. E. Horve and M. Schiller. *J. Applied Physiol.* 5: 51, 1952.

This study presents graphs of the average height and weight of the boys and girls in the Volksschule and Oberschule, at Stuttgart, Germany, from 1915 to 1948. This covers a long period including two world wars, several booms and depressions, war exhaustion and beginning recovery. Volksschule children represent low income families and Oberschule those of higher income brackets. When conditions of nutrition and environment improved, the height and weight of Volksschule children increased more than that of the other group. Both height and weight were reduced during food rationing in the war. Children of the same age were shorter in stature in the period 1914–20 (World War I) than in 1939–45 (World War II). The rate of change of height was greater than in weight. At the start of World War II the rate of growth of all school children was retarded. Increases in height and weight began after the end of the war, with some retardation during the shortage of food due to drought in 1946–47. The point is well made that environment and food shortage make measurable changes in increase of height and weight of children. However, caution is properly expressed that other factors such as poverty, stress, and poor hygienic conditions may play a role. Futhermore, data are not at hand to prove that if a child fails to grow at one time he will be seriously affected at that time or later in life.—M. J. OPPENHEIMER

The laboratory diagnosis of malnutrition is notoriously unreliable. One of the more recently introduced procedures is the serum cholinesterase level. However, in malnourished children, the range of cholinesterase values was found to be similar to that of normal children. This differs from the results obtained in studies on adults.

Relation of Serum Cholinesterase to Nutritional Status of Adolescents. J. P. Saunders, H. R. Sandstead, R. E. Butler, and O. Mickelsen. *J. Nutrition* 47: 191, 1952.

It has been previously reported that the mean serum cholinesterase levels in 82 German workers subsisting on civilian rations in 1946, and in 57 with nutritional edema, were about half the normal values. When the malnourished men were given enough food to produce a considerable increase in body weight, the serum cholinesterase approached normal. A subsequent restriction of food and loss of body weight reduced the cholinesterase levels again. These findings led the authors of these observations to conclude that the serum cholinesterase level was a delicate index of the state of nutrition of any group of men in Germany at that time.

In this investigation, in 119 children no useful relation was found between serum cholinesterase levels and hemoglobin, serum carotene, degree of underweight, physical signs indicative of malnutrition, or general appearance from a nutritional standpoint. The lower the body weight in relation to the standard weight (from height-weight tables), the higher was the serum cholinesterase level, which is the reverse of the relationship previously reported. On the other hand, the higher the serum carotene level, the higher was the serum cholinesterase. Since the range of cholinesterase levels encompassed by the regression line was very small in both cases, and the range of cholinesterase levels in normal children was as great as that in malnourished children, the application of this enzyme level to nutrition studies is of dubious value among populations at nutritional levels similar to those investigated in this study.—B. SURE

Severe malnutrition is capable of producing alterations in the metabolism of the infant. Refeeding programs in these patients result in further abnormalities, particularly with reference to hepatic function. Similar findings in undernourished adults have been reported.

Nutritional Recovery Syndrome. F. Gomez, R. Ramos Galvan, and J. Cravioto Muñoz. *Pediatrics* 10: 513, 1952.

The authors report an interesting sequence of events which occurs during recovery of infants and children from severe malnutrition. The patients reported were studied in an infants' hospital in Mexico.

The infants had been severely malnourished for long periods of time. Some two or three weeks after being restored to a more adequate diet the following symptoms and laboratory findings began to appear: edema, hepatomegaly, abdominal distention, portal vein hypertension, as indicated by ascites, and increased conspicuousness of the superficial veins on the abdomen and thorax. Hypertrichosis of the forehead, back, and thighs and eosinophilia also were found. Examination of the serum proteins revealed a hypergammaglobulinemia. Biopsy of the liver revealed fatty changes, and liver function tests were reported abnormal. The paper gives excellent illustrations of the phenomena described and photomicrographs of the fatty infiltration of the liver. Serial biopsies of the liver were done to trace the changes during the patient's course. The authors were unable to provide a satisfactory explanation for the sequence of events. The paper should be of interest to those interested in the pathogenesis of fatty liver. —C. D. MAY

The development of liver disease may be associated with the prolonged feeding of diets which are low in protein content. An interesting analysis of this problem is discussed with reference to observations made on Jamaican children.

Some Observations on the Diet of Jamaican Children, with Particular Reference to Liver Disease. K. Rhodes. *Brit. J. Nutrition* 6: 198, 1952.

The object of this investigation was to correlate the liver disease of Jamaican children with their inadequate diet. During this study 115 cases of liver disease were investigated, 90 liver biopsies were performed on 58 cases by the needle technique, and, in addition, 10 post-mortem specimens were examined. Though the majority of these children looked chubby and well nourished, all had an enlarged liver and some had enlargement of the spleen with ascites and occasionally edema of the legs. The diet of each of the children suffering from liver disease was inquired into, but the food intake of ten children was studied in more detail and compared with that of five healthy controls. Their ages varied from 9 months to 8 years, the majority being between 9 months and 3 years. Eight were male.

The calculated carbohydrate and calorie intake did not differ appreciably in the two groups, but the daily protein and fat intake of the children with liver disease was invariably much lower than that of the healthy group. The children on the low protein-fat diet had severe hepatic fibrosis with splenomegaly and did not thrive. Eight of the 10 children with liver disease derived their animal protein from a single source only, 7 from condensed milk and 1 from fresh cow's milk. Of the remaining 2 cases, 1 had a small quantity of beef in addition to condensed milk, and the other a small amount of beef and egg. Of the healthy children, 1 had all available protein from condensed milk alone. The remaining 4 children had a combination of sources, including cow's and condensed milk, eggs, beef, and fish. The healthy children averaged 3.2 different sources of animal protein and the sick ones 1.3. There was also a difference in the types of vegetable proteins taken by the two groups. In the cases with liver disease, the pattern was that of white bread, maize meal and green banana, whereas the control cases had more varied sources with greater protein

content, such as whole wheat bread, rice, vegetables, and fruit.

From the above results cited it is evident that the underlying cause of liver disease in Jamaican children is inadequate and poor quality protein in the diet.—B. SURE

Several recent reports have described interesting experiences in infant feeding. The techniques of feeding and the nutritional requirements of premature infants have been carefully appraised. Of particular interest is the reduction in mortality in breast-fed infants.

The Feeding of Premature Infants. V. M. Crosse. *Brit. J. Nutrition* 6: 230, 1952. (Proc. of the Nutrition Soc.)

The general principles of infant feeding have to be modified for premature infants, because of their physical handicaps and their greater nutritional requirements. If the sucking and swallowing reflexes are completely absent, gavage or bottle-feeding must be used, but weakness or rapid exhaustion of the reflexes may be overcome by giving small feeds or divided feeds with 5-minute rest during the feed.

In a Birmingham survey of 1380 premature babies, feeding appeared to have little effect on the neonatal mortality, but between the ages of 1 and 6 months, the mortality in breast-fed infants was 0.8 per cent and in artificially fed infants, 5.6 per cent.

Calories. Before the age of 2 weeks the caloric requirement is very small because the basal metabolism is low and activity is relatively slight. After the first 2 weeks an allowance of from 55 to 60 cal./lb. body-weight daily maintains a satisfactory rate of growth, provided that the calories are given in a suitable form and that the infant is cared for in a suitable environment. Overfeeding, with its great dangers, must be avoided during the first 2 weeks of life. The requirements are small and the danger of underfeeding is very slight.

Protein. The smallest premature babies grow about twice as fast as full-time babies, and may require twice as much protein. A daily allowance of from 2.0 to 2.7 Gm. protein/lb. body-weight is recommended for premature infants. Because of the low protein content of human milk, various high protein feeds have been tried, such as human milk with added protein and various modifications of cow's milk.

Fat. There is difficulty in the utilization of fats during the first few months of life; therefore, high fat feeds should be avoided during that period. As the infant matures, the utilization of fat improves.

Carbohydrate. Premature infants utilize carbohydrates to a greater degree than full-term babies, and tolerate high proportions of nonfermentable sugars, such as cane or beet-sugar, or dextri-maltose. High percentages of glucose or lactose may cause diarrhea.

Fluid. Water accounts for a larger percentage of the weight at birth than in full-term babies. The optimum daily fluid allowance after the first week of life lies between 2 and 3 oz./lb. body-weight. The volume of human milk that supplies the necessary calories furnishes the necessary fluid also. If cow's milk mixtures are used, they should not supply more than 24 cal./oz., if the intake of a safe amount of fluid is to be insured.

Mineral Salts. Human milk has a low content of calcium and phosphorus. Cow's milk has a high content of both. An adequate supply of vitamin D is necessary for full utilization of the available Ca and P. Human milk contains little iron, and cow's milk still less, but no advantages have been observed by giving extra iron before the age of 4 to 6 weeks. After that age, administration is beneficial to prevent an iron-deficiency anemia.

Vitamins. The needs of the premature baby are greater than those of the full-term baby, because the antenatal store is small, postnatal growth is more rapid, absorption of fat-soluble vitamins is poor, the need for vitamin C is increased with the use of high protein diets, and the need for vitamin D is increased by the extra needs for Ca and P. The following allowances are recommended:

Vitamin K, 10 mg. daily until 2 days after commencement of feeding; vitamin B complex, from the commencement of feeding (requirement unknown); ascorbic acid, from 50 to 100 mg. daily from commencement of feeding, the large dose being given to infants on high protein feeding; vitamin D, from 3000 to 5000 International Units daily from the end of the second week, or a massive dose commencing at the age of 2 weeks and repeated at monthly intervals; vitamin A, from the age of 2 weeks (requirement unknown).

It is apparent from the above recommendations that there is a great need for definite information on the vitamin A and vitamin B complex requirements of the premature infant.—B. SURE

A comprehensive evaluation of the composition of human breast milk explains the advantages of the feeding of this substance to infants. In addition to being an excellent food, its value is enhanced by the presence of antibodies in it.

Composition of Human Milk and Factors Affecting it. M. Gunther. *Brit. J. Nutrition* 6: 207, 1952. (Proc. of the Nutrition Soc.)

The composition of breast milk is of interest primarily because it is the most satisfactory food for the baby. The proteins of mature human breast milk contain 0.7–0.8 Gm. lactalbumin and lactoglobulin in 100 ml., rather more than cow's milk (0.5 Gm. per 100 ml.) but the casein (0.4–0.5 Gm./100 ml.) is much less than that of cow's milk (3.0 Gm./100 ml.). The nonprotein nitrogen is slightly less than in cow's milk, but the free amino acids are about the same in amounts and proportions in both. The evidence of a large survey in 1950 shows, however, that in England the breast-fed child has spe-

cific advantages. Even when allowance had been made for birth weight and body weight, the breast-fed baby was shown to walk 10 days earlier than the bottle-fed and to have received an immunity to measles. The author concludes from the observations on the protection against measles that possibly the globulins of human milk are broken down by digestion sufficiently to lose their antibody pattern and yet retain some linkages that assist the baby to reconstruct human γ-globulins.

The composition of breast milk depends mainly on the phase of lactation. Whereas the contents of protein, fat, and sugar are virtually uninfluenced by diet, the concentration of vitamins depends partly on what the mother eats.

Vitamin D is present in very small quantity in breast milk. Supplements of vitamin D in the maternal diet do not seem to alter the calcium or phosphorus in breast milk, or the content of the vitamin except in massive doses, but the mother needs adequate amounts of this vitamin for her own safeguard. The thiamine in breast milk increases slowly in the first days of lactation, from 3 μg./100 ml. on the third to 9 μg./100 ml. on the tenth. After the fifth week there is no consistent trend. The content responds slowly to the amount of the vitamin eaten, but does not rise above 20–35 μg./100 ml. The riboflavin content, however, is altered in a matter of hours by the mother's food and has no maximum level. Riboflavin is present on the average of 26 μg./100 ml. in the milk of English women. The concentration of ascorbic acid in breast milk is generally found to be 4 mg./100 ml. The maximum concentration can be raised to 10 mg./100 ml. when the mother is taking 300 mg. daily.

Of the mineral elements, those of principal interest are calcium, phosphorus, sodium, potassium, chlorine, and iron. The calcium and phosphorus of breast milk vary greatly in concentrations in different women, although the level of concentration by one woman is relatively constant. The Ca content ranges between 19 and 40 mg./100 ml. and the P between 10 and 20 mg./100 ml. There is less sodium and potassium in human than in cow's milk, the range being from 11 to 19 mg./100 ml. for sodium and from 48 to 65 mg./100 ml. for potassium, about one-third of the concentration in cow's milk. The iron ranges from 0.09 to 0.2 mg./100 ml., and the copper from 0.5 to 0.6 mg./ml., the values in both sources being greater than for cow's milk. Chlorides increase when the breast is lax. Early in the day the concentration is less than later, and it is also less when the milk flow is abundant than when it is scanty. The range is from 30 to 150 mg./100 ml.—B. SURE

Meat supplementation in the diet of infants appears to have a salutary effect, although the data presented do not seem to be conclusive.

Evaluation of Meat in the Infant Diet. H. M. Jacobs and G. S. George. *Pediatrics* 10: 463, 1952.

This paper presents a study comparing infants fed meat as a supplement to their diet with others fed a standard hospital diet without the meat supplement. No attempt was made to keep the caloric intake equal in the two groups and no data are provided concerning the actual quantitative intake of protein from all sources in each group. The assumption is made that the protein intake in the meat-fed group was actually greater, but data are not provided which would demonstrate this. The conclusions, then, are based on the assumption that differences in the groups may be attributed to the role of meat in the diet. The observed effects were obtained only if the infants were fed meat under two months of age. When supplementation was started later, no discernible differences were noted.

Data are provided indicating a slight improvement in weight gain, total protein and hemoglobin levels, and a lower incidence of infections in the meat-fed group. The data provided do not seem adequate for a recommendation for the inclusion of meat in the diet of infants as a necessary or advantageous practice. There is no evidence of any harmful effects of adding meat to the small infant's diet. It must be remembered that allergic reactions to protein foods are possible. It would be noted that the meat-supplemented group also regularly obtained a higher caloric intake providing the diets were completely consumed.—C. D. MAY

FOLIC ACID

Pteroylglutamic acid (folic acid) is a substance of wide importance. Studies on the availability, absorption, and utilization of folic acid are reported in the following papers.

The Utilization of Folic Acid Given by Mouth. G. H. Spray and L. J. Witts. *Clin. Sc.* 11: 273, 1952.

The oral administration of 1 mg. pteroylglutamic acid (PGA, or folic acid) led to an increase in the plasma folic acid concentration at the end of the first hour. Normal values are reached after 5 or 6 hours, and between 2 and 20 per cent of the dose is excreted in the urine in 5 or 6 hours. Untreated patients with pernicious anemia show a much smaller increase in folic acid concentration in the plasma and a very small (5 per cent or less) urinary excretion. When patients with pernicious anemia are treated with liver extract or vitamin B_{12}, the response to oral folic acid is normal.

These results suggest that there is either an impaired absorption or increased utilization of folic acid in pernicious anemia in relapse. The authors favor the latter suggestion and show that the results are consistent with the hypothesis of Vilter *et al.* Shortage of vitamin B_{12} in pernicious anemia is supposed to produce an increased demand for folic acid.—S. O. WAIFE

Folic acid conjugates present in vegetables and meat require the presence of a conjugase enzyme system for the release of free folic acid. These may be factors of considerable clinical importance.

The Utilization of Folic Acid from Natural Sources. G. H. Spray. *Clin. Sc.* 11: 425, 1952.

Normal subjects who are given by mouth a quantity of yeast extfact containing at least 1 mg. of folic acid, mostly in the conjugated form, may show small increases in the concentration of folic acid in the plasma and in the amount of the substance excreted in the urine. Other subjects may show no significant increase. These results are in striking contrast to the effects observed when normal people are given 1 mg. of pure pteroylglutamic acid (folic acid) by mouth. This difference may be due to several causes. Folic acid might be absorbed more slowly when present in a crude mixture than when given as pure pteroylglutamic acid, or folic acid in natural materials perhaps may be poorly absorbed because it is combined with proteins or other substances not split by gastric or duodenal enzymes.

This observation suggests that only a small proportion of folic acid present in food is absorbed from the gut.—S. O. WAIFE

The Haemopoietic Activity of Folic Acid Treated with Xanthine Oxidase. W. Jacobsen and P. M. Good. *Quart. J. Med.* 21: 1, 1952.

The treatment of folic acid with the enzyme xanthine oxidase resulted in the formation of a substance which had greater hemopoietic activity in pernicious anemia patients than did folic acid itself. The possibility exists that xanthine oxidase may function in the conversion of folic acid into the *Leuconostoc citrovorum factor* (folinic acid).—C. R. SHUMAN

It is believed that the folic acid-citrovorum factor (folinic acid) system is essential for the synthesis of nucleoprotein, through the formation of the thymidine portion of desoxyribonucleic acid. It is also active in the formation and utilization of single carbon units in cellular biosynthesis. Certain structural analogues of pteroylglutamic acid, for example aminopterin, have been shown to antagonize its metabolic actions. In diseases such as leukemia there appears to be a high metabolic demand for folic acid. Therefore, the use of the antagonist compound is of interest in patients with this disease.

The Nutritional Status of Folic Acid in Persons with Leukemia and Its Possible Relation to Effects of Aminopterin Therapy. M. E. Swendseid, A. L. Swanson, M. D. Meyers, and F. H. Bethell. *Blood* 7: 307, 1952.

Folic acid antagonists have been used since 1948 in the treatment of leukemia. Prolonged remissions have been obtained in children with the acute form of the disease. Persons with chronic leukemia have responded poorly and have developed severe folic acid deficiency manifestations. Since the nutritional status of the subject prior to antimetabolite therapy may determine his systemic response to such a drug and the speed and frequency with which he develops deficiency manifestations, the authors studied the folic acid nutritional status of 18 persons with chronic leukemia and 13 with acute leukemia. Each patient received a test dose of 5 mg. of folic acid and the per cent of this test dose excreted in the urine in the following 24 hours was determined. Normal persons excreted from 25 to 35 per cent; those with acute leukemia from 14 to 33 per cent; and those with chronic leukemia from 5.5 to 26 per cent. Seven persons with chronic leukemia, but none with the acute form of the disease excreted less than 15 per cent of the test dose. The lowest excretion rates were found in patients with chronic lymphatic leukemia. These data suggest that persons with chronic leukemia have a high metabolic requirement for folic acid, probably because of the large amount of this vitamin incorporated into the large numbers of leukemic cells. Thus there is less vitamin available for other cells of the organism and a metabolic antagonist rapidly induces severe deficiency manifestations. These data, however, have no bearing on the therapeutic effects of an antagonist such as aminopterin on the leukemic process.—R. W. VILTER

The Metabolic Displacement of Folic Acid by Aminopterin. Studies in Leukemic Patients. M. E. Swendseid, A. L. Swanson, S. Miller, and F. H. Bethell. *Blood* 7: 302, 1952.

Two milligrams of aminopterin were administered daily to nine patients with various types of leukemia. The amount of folic acid excreted after a test dose of 5 mg. was determined before and 6–10 days after the withdrawal of the antagonist. After aminopterin, the amount of folic acid excreted was increased 2–3 fold over the value previously obtained. Data are given also on the excretion of aminopterin during the period when 1 or 2 mg. per day were administered.

The amount of aminopterin excreted varied from patient to patient, but in all cases, considerable was retained, the largest amount in patients with chronic granulocytic leukemia. Excretion of the drug continued for at least 6 days after the last dose was administered. Following aminopterin therapy there was an increase in folic acid excretion, suggesting that the aminopterin had displaced folic acid, an effect which persists for a considerable length of time. It is probable that this effect occurs because aminopterin interferes with the conversion of folic acid to the citrovorum factor.—R. W. VILTER

The following conference provides the reader with a comprehensive knowledge of folic acid metabolism, the effects of folic acid antagonists, and the present status of the latter compounds in the treatment of leukemia.

Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia. W. Shields and S. Murray, Chairmen. *Blood* 7: Supplement 97: 190, 1952.

Since 1947 a great body of knowledge has been accumulated concerning the effects of the folic acid antagonists on the cells of acute leukemia. Nutrition and studies in the growth requirements of cells and the inhibition of malignant tumors by growth antagonists and antimetabolites impinge in this field of endeavor. This knowledge is summarized concisely in the minutes of this conference. All facets of the problem are covered, including the chemical structure of these antagonists, the probable biological action of antagonists like aminopterin in suppressing the formation of the citrovorum factor, the metabolic action of the folic acid coenzyme in facilitating the transfer of single carbon units for the formation of the purine ring, for the methylation of pyrimidines, and for the formation of serine and methionine. There is an excellent discussion of the biological effects of the folic acid antagonists on mouse leukemia and mouse tumors, and the development of aminopterin-resistant tumor cells in these animals. Statistics are tabulated from all research centers in the United States on clinical experiences with these agents in the therapy of acute leukemia in children and adults. Rates of remission vary somewhat, but, by and large, they are higher in children than in adults, best in acute lymphatic leukemia, and worst in the acute monocytic type. No cures have been attained, but remissions for as long as 24 months are reported. For instance, in 190 patients with acute leukemia treated for more than 21 days, 28 per cent had complete remissions, 22.1 per cent had partial remissions, 31.6 per cent were failures, and the rest fitted into intermediate categories. The experience in the past year has not changed the picture appreciably, though with ACTH or cortisone, a somewhat greater number of remissions are possible. Though we are still far from a satisfactory method for the control of leukemia, at least methods are now available which will temporarily reverse the progress of a disease previously considered irreversible.—R. W. Vilter

The following reports discuss the relative inadequacy of folic acid as a form of therapy for pernicious anemia. As usual, vitamin B_{12} was found to be effective. However, in megaloblastic anemias associated with infection, folic acid is essential.

Parenteral B_{12} Folic Acid Therapy in Pernicious Anemia. E. H. Sanneman, Jr., and M. F. Beard. *Ann. Int. Med.* 37: 755, 1952.

This report deals with the administration of a mixture of vitamin B_{12} and folic acid parenterally to 8 patients with proved pernicious anemia whose blood counts had tended to fall while on maintenance therapy with parenteral vitamin B_{12}. Seven of these 8 patients had a poor dietary history. There was absolutely no hematologic response to the added folic acid in any of these patients, and actually 7 of the 8 experienced insignificant drops. The authors' conclusions were that the cause of the decline hematologically was not a folic acid deficiency, but was probably related to a more complex deficiency state.

This report verifies the generally accepted view that vitamin B_{12} alone is completely adequate in the therapy of pernicious anemia *per se*. That other nutrients are essential for normal hematopoiesis is of course recognized, and if these are lacking anemia will result as it would in a normal person. As yet there is no clear-cut evidence that hematologic relapse of the erythrocyte-maturing factor (E.M.F.) deficiency variety will occur in patients receiving adequate amounts of vitamin B_{12}. This is different, of course, from the hematologic relapse which occurs in patients with P.A. treated with folic acid alone. In this instance, evidence of E.M.F. deficiency is present in the bone marrows.—J. F. Mueller

The Reticulocyte Crisis Produced by Folic Acid in Pernicious Anemia in Relation to Initial Blood Levels. B. Emilio. *Acta Vitaminol.* 6: 16, 1952.

In the treatment of pernicious anemia with oral liver or parenteral liver extract, an inverse relationship between reticulocytosis and initial blood values has been demonstrated by various observers. In the present study, folic acid alone was given to patients with P.A., in order to compare the reticulocyte response to that achieved with liver. Thirteen subjects were studied, 12 of whom had previously received liver extracts or oral liver; the remaining subject had not been treated before. Dosage varied between 15 and 20 mg. of folic acid daily, over a period ranging from a maximum of 20 days to a minimum of 6 (total amount: 285–760 mg.).

As with liver, an inverse relationship between initial erythrocyte values and ultimate reticulocyte response was observed—a relationship which was linear with respect to absolute reticulocytosis and parabolic with respect to relative reticulocytosis. However, though the response paralleled that achieved with liver (the lower the initial level of circulating erythrocytes, the higher the level obtained in the reticulocyte crisis), the levels reached with folic acid were definitely lower than those obtained with liver.—C.-J. Howell

Infection as Cause of Folic Acid Deficiency and Megaloblastic Anemia. C. D. May, C. T. Steward, A. Hamilton, and R. J. Salmon. *Am. J. Dis. Child* 34: 718, 1952.

Infants with megaloblastic anemia frequently have a history of infection and ascorbic acid deficiency. Megaloblastic anemia was induced experimentally in monkeys by producing abscesses with intramuscular injections of turpentine. It was found that the content of folic acid compounds was reduced in the liver and megaloblastosis could be eliminated from the marrow by folic acid but not by vitamin B_{12} or

ascorbic acid. This leads to the conclusion that infection can cause a deficiency of folic acid compounds.

The practical consequences of this finding are that normal infants on usual feeding regimens, including adequate ascorbic acid, do not require supplementary vitamin B_{12} or folic acid compounds; however, sick infants, suffering from infection, ascorbic deficiency, and other pathological circumstances, may have an increased requirement of vitamin B_{12} and folic acid. In cases of severe and prolonged infections, it would probably be wise to include additional amounts of vitamin B_{12} and folic acid during the treatment of the infection or the immediate convalscent period.— S. O. WAIFE

The megaloblastic anemia and scorbutic state induced in animals by diets inadequate in ascorbic acid and folic acid content represent an excellent tool for the study of the metabolic interrelationships involving these vitamins. Folic acid requirements are elevated in the presence of ascorbic acid deficiency.

Experimental Megaloblastic Anemia and Scurvy in the Monkey. IV. Vitamin B_{12} and Folic Acid Compounds in the Diet, Liver, Urine and Feces and Effects of Therapy. C. D. May, A. Hamilton, and C. T. Stewart. *Blood* 7: 978, 1952.

Monkeys fed milk diets devoid of ascorbic acid and low in folic acid regularly develop a severe deficiency of folic acid compounds and a megaloblastic anemia as a complication of scurvy. Under these experimental conditions, the concentrations of vitamin B_{12}, folic acid, and folinic acid (citrovorum factor) were determined in the diet, liver, urine, and feces and compared with the appearance of the bone marrow. No deficiency in vitamin B_{12} could be determined, nor was there a hematopoietic response to therapy with vitamin B_{12}. Fecal content of folic acid did not change significantly and urinary excretion of folic acid was not a satisfactory indication of tissue stores. The levels of folic and folinic acids in the liver were the best indications of these stores and megaloblastosis did not occur unless the folinic acid level in the liver was low. Conjugated folic acid orally increased the liver folic acid but not folinic acid, and the marrow remained megaloblastic. The same compound, given parenterally, increased the folinic acid but not the folic acid levels in the liver, and megaloblastosis disappeared. Folic acid or *l*-ascorbic acid given orally elevated the liver folic and folinic acid levels and eliminated megaloblastosis. *D*-Ascorbic acid and *d*-glucoascorbic acid did not have this effect, nor did B complex vitamins, brewers' yeast, aureomycin, cortisone, choline, para-aminobenzoic acid, biotin, or inositol.

From these data the authors conclude that ascorbic acid is not essential for the normal metabolism of folic acid compounds (*i.e.*, conjugates parenterally were effective and folic acid was converted to folinic acid in the absence of ascorbic acid), but that the requirement for folic acid compounds is increased in scurvy, presumably through some type of stress reaction. Perhaps it is through such a mechanism, perhaps through another, that ascorbic acid increases the folic and folinic stores in these monkeys.—R. W. VILTER

Experimental Nutritional Megaloblastic Anemia and Scurvy in the Monkey. III. Protoporphyrin, Coproporphyrin, Urobilinogen and Iron in Blood and Excreta. E. C. Proehl and C. D. May. *Blood* 7: 671, 1952.

This paper presents additional data on the hematologic status of monkeys during the induction of scurvy and megaloblastic anemia by diets devoid of ascorbic acid and containing only a small amount of folic acid. After 30 days without ascorbic acid the monkeys are classified as ascorbic acid deficient. When clinical signs of scurvy appear the animals are classified as scorbutic (normoblastic). After about two weeks of scurvy, the marrow becomes megaloblastic and then the animals are classified as scorbutic (megaloblastic). With the onset of scurvy, hemoglobin levels fell rather abruptly, plasma iron decreased, and erythrocyte protoporphyrin rose. Little additional change occurred when the marrow became megaloblastic. On treatment with folic or folinic acid there was reticulocytosis in the erythrocyte protoporphyrin and coproporphyrin. Plasma iron levels continued to fall and there was intermittent elevation of the fecal urobilinogen levels probably coincident with tissue hemorrhages. The scorbutic state, of course, was not influenced by the folic or folinic acids. When a similar monkey with megaloblastic anemia and scurvy was treated with ascorbic acid, the megaloblastosis disappeared slowly, reticulocytosis occurred and was followed by a rapid rise in hemoglobin. Erythrocyte protoporphyrin and coproporphyrin increased temporarily. No data are available on the effect of ascorbic acid on plasma iron levels. However, monkeys maintained on scorbutigenic diets and given folic acid prophylactically developed scurvy in the usual time but the marrows remained normoblastic even though anemia developed. The plasma iron decreased. No data are given on the response of plasma iron in these monkeys to ascorbic acid treatment. The authors do indicate that neither orally administered iron at a dose of 25 mg. a day nor intravenous saccharated oxide of iron in doses of 30 or 50 mg. intravenously per day influenced the plasma iron levels.

The authors interpret these data as indicating that ascorbic acid deficiency increases the requirement for folic acid and decreases the available stores of iron, possibly by decreasing absorption from the G.I. tract and by leading to hemorrhages externally. They find no evidence to support any other function for ascorbic acid in hematopoiesis. They interpret the increase in urobilinogen levels as indications of tissue hemorrhage, an additional cause for rapid hemoglobin decrease. They do not give any explanation as to why

iron supplements of 25 mg. a day orally even in the absence of ascorbic acid do not serve to maintain serum levels since other reducing substances aside from ascorbic acid also enhance iron absorption. There is no explanation either as to why intravenous iron has no effect on the serum iron levels, though the authors suggest that the stress of the scorbutic state may be the cause. In addition the daily increase in the hemoglobin which occurs in scorbutic megaloblastic monkeys treated with ascorbic acid is over 0.3 Gm. per cent per day, a figure which is usually considered to be the maximum which one may expect when iron deficiency hypochromic anemia is treated with parenteral iron. If ascorbic acid has no direct effect on hematopoiesis and induces hemoglobin formation only by stopping hemorrhages and making more iron available (in previous papers these authors state that ascorbic acid leads to only gradual conversion of megaloblastic bone marrows to normoblastic type over a period of 7 to 11 days), it is difficult to explain the striking reticulocytosis and the hemoglobin increase which is calculated to be about 0.37 Gm. per 100 cc. per day.

It is interesting to compare the anemia usually observed in adult scurvy with this monkey anemia. In persons with adult scurvy the anemia is usually normocytic or slightly macrocytic and normochromic. There is moderate reticulocytosis. Serum iron levels are normal or slightly elevated. The bone marrow is hypoplastic or normally cellular and the urine and fecal urobilinogen levels are high. Only rarely may one find the appearance of megaloblastic maturation arrest in the bone marrow. When vitamin C is administered hemorrhages cease and fecal urobilinogen levels fall to normal. Reticulocytosis decreases, but within a few days the bone marrow becomes hyperplastic and normoblastic. Hemoglobin regeneration takes place rapidly. This course of events occurs with or without previous treatment with folic or folinic acids. Such patients do not have evidence of iron deficiency, few of them have much external blood loss, and many of them have little in the way of hemorrhage into the tissues. It would seem that there are additional functions of ascorbic acid in hematopoiesis which have not yet been elucidated by animal experimentation and are very difficult to establish in the persons with adult scurvy because of the multiplicity of factors which seem to be involved.—R. W. VILTER

Although intervitamin antagonism is not clearly understood, certain curious relationships have been discovered, as in the following paper.

Studies on the Relationship between Pteroyglutamic Acid and Thiamine. Functional Anatomical Aspects of Thiamine Hypervitaminosis Treated with Various Quantities of Folic Acid. F. Bertolani and R. Lorenzini. *Acta Vitaminol.* 6: 10, 1952.

In pigeons on a thiamine-deficient diet, the administration of doses of folic acid in excess of 0.5 mg. (irrespective of the amount) caused the signs of thiamine deficiency to appear earlier than in the controls; nor did the pigeons receiving folic acid survive as long as the controls.

In both groups of beriberic pigeons, the administration of vitamin B_1 produced a rapid disappearance of deficiency symptoms and return to normal.

The precocious appearance of deficiency signs in these pigeons confirms previous evidence of folic acid-thiamine antagonism. The regression of the signs with thiamine administration is at variance with results obtained in certain previous experiments, in which experimental beriberi, aggravated by folic acid administration, was reported to be irreversible.—C.-J. HOWELL

NUTRITION AND CIVIL DEFENSE

The following papers are abstracted together. They represent the results of deliberations on the above subject between official delegates of the Governments of Canada, the United Kingdom, and the United States of America conducted in London, November 26 to December 13, 1951. The papers, published in Public Health Reports, volume 67, 1952, include the following specific titles:

Scientific Problems in Food Defense, N. C. Wright, *Pub. Health Rep.* 67: 614, 1952.

Need for Research in Nutrition, C. G. King, *ibid.* 67: 618, 1952.

Nutrition Lessons of the Berlin Blockade, H. E. Magee, *ibid.* 67: 622, 1952.

Food Sanitation in Civil Defense, W. B. Rankin, *ibid.* 67: 627, 1952.

A Safe Water Supply in Civil Disaster, G. E. McCallum, Wm. E. Holy, and H. Ludwig, *ibid.* 67: 631, 1952.

Milk Control Planning for Civil Disaster, G. E. McCallum and J. D. Faulkner, *ibid.* 67: 635, 1952.

Food Sanitation Problems in Emergency Feeding, G. E. McCallum, J. D. Faulkner, and S. E. Loelz, *ibid.* 67: 639, 1952.

Handling of Meat in an Emergency, C. H. Pals, *ibid.* 67: 642, 1952.

Dietary Standards in the United States, L. A. Maynard, *ibid.* 67: 784, 1952.

Family Food Consumption Studies, C. M. Coons, *ibid.* 67: 788, 1952.

Nutritional Problems and Civil Defense, Sir Jack Drummond, *ibid.* 67: 857, 1952.

Food Supply and Emergency Feeding in Civil Defense, P. B. Murphy, L. Trainer, and J. M. Hundley, *ibid.* 67: 860, 1952.

Necessary Foods for Emergency Feeding, J. M. Hundley, *ibid.* 67: 864, 1952.

Special Feeding Problems in an Emergency, R. E. Butler, *ibid.* 67: 867, 1952.

Feeding of Mothers and Children Under Emergency Conditions, M. M. Heseltine, *ibid.* 67: 872, 1952.

A thoughtful consideration of administrative and scientific aspects is in evidence. The prime problems are related to atomic attack upon large cities. It is recommended that those interested read the articles in their original form. The bibliographies attached to most of the articles are comprehensive.

There were three major considerations:

(1) *Emergency Feeding:* The value of decentralized municipal administration was emphasized, together with the importance of recruiting and training volunteer and other individuals. There were comments upon the need to improvise fuels and cooking materials as well as full utilization by whatever legal means could be found to use commercial caterers, restaurateurs, and others. It is apparent that an adequate supply of safe water for drinking as well as for cleansing and sterilization is a difficult problem after it becomes contaminated with radioactivity. There was general agreement that at least for the type of acutely bombstruck individuals being discussed a hot sweet drink is a "must" item to help relieve shock and restore morale and public order. It was felt that a good hot meal and not sandwiches should be provided within a few hours of a major emergency, largely because of its effect upon morale.

(2) *Food Administration:* Among the unsolved problems is the matter of immediate supply of fresh bread and milk and in particular the prevention of glass damage to foods. This was a very serious cause of food loss in Britian during the last war.

(3) *Scientific Aspects:* It was held that vitamin deficiencies would not occur in a well-nourished population in less than a month and that no special precautions need be taken in this regard even for infants and nursing mothers. The assessment of special caloric needs for heavy workers met no particular agreement.

It was felt that food in *unbroken* containers should be safely decontaminated from radioactivity. Proper monitoring was urged as a guide in assessment of safety. Additional importance was placed upon the need for research in proper methods of dehydration and concentration of foods in order to reduce space requirements in stockpiling and to provide foods with improved palatability, ease of reconstitution, and keeping quality. One thing which emerges clearly from this conference is the fact that no universal rules can be applied when so much of dietary habits are cultural rather than nutritional.

In considering certain additional requirements for nutritional research as it relates to civil defense, it was pointed out that much basic nutritional information concerning burns, traumatic shock, and ordinary radiation sickness has yet to be gathered. The need for learning how to teach individuals to conserve work output has received little attention.

Of the "Big Three" (AW, BW, CW) little of the Conference was devoted to BW (biological warfare), i.e., the problems of feeding a population in the face of infection disseminated by hostile agents. The nutritional aspects of CW (chemical warfare) have been discussed many times previously at least in so far as cutaneous and respiratory viritants are concerned. There appears to be little applied field knowledge of the somewhat newer nerve gases.

These international conferences relate to food supply, nutrition and the use of atomic weapons by a hostile group. It would seem likely that national, state, and local briefing conferences will be called from time to time. There will be considerable challenge to all services relating to nutrition and not merely for the food technologist.—A. J. Steigman

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ITEMS OF GENERAL INTEREST

Dietary Cholesterol and Atherosclerosis. C. Moses. *Am. J. M. Sc.* 224: 212, 1952.

From the accumulated data in the literature, it seems apparent that cholesterol plays a major role in the pathogenesis of atherosclerosis. It has also been demonstrated that the body can synthesize cholesterol within various tissues, including the arteries, in the absence of exogenous cholesterol. Moderate increases or decreases in dietary cholesterol failed to exert any significant effect upon serum cholesterol levels. However, practically complete elimination of all dietary cholesterol and other lipids, including vegetable oils, is necessary in order to achieve a reduction of serum cholesterol values. There is great difficulty in providing adequate protein and calories in the absence of dietary fat and the unpalatability of such diets renders them virtually useless. Observations as to the effect of other dietary components such as protein, phospholipid, or certain vitamins upon the physical state of circulating cholesterol are warranted.—C. M. Shuman

Observations on the Fate of Ingested Cholesterol in Man. M. W. Biggs, D. Kritchevsky, D. Colman, J. W. Gofman, H. B. Jones, F. T. Lindgren, G. Hyde, and T. P. Tyon. *Circulation* 4: 359, 1952.

Tritium (H^3)-labeled cholesterol was used to study the absorption and turnover of cholesterol in various blood compartments of four atherosclerotic patients. The cholesterol was fed in Wesson oil emulsified in whole milk or crystalline cholesterol dispersed in milk. Absorption of cholesterol administered in this manner was slow, with the peak specific activity being reached in 36 to 72 hours. By ultracentrifugation it was found that the cholesterol of the various lipoprotein fractions of different S_f rates interchanges rapidly. The specific activity and interchange rates of the esterified cholesterol were lower than those of free cholesterol. Equilibrium of red blood cell chol-

esterol with free serum cholesterol *in vivo* was demonstrated. In one autopsied patient, the quantity of labeled cholesterol found in the aorta indicated that an appreciable amount arose from the serum as a result of interchange of aortic and serum cholesterol prior to death.—C. R. SHUMAN

Correlation of Serum Potassium Concentrations with the Blood Pressure in Rats Fed a Potassium-Deficient Diet. S. M. St. George, S. C. Freed, and R. H. Rosenman. *Circulation* 4: 371, 1952.

The feeding of a potassium-deficient diet was found to produce hypotension in rats. The serum potassium levels of the animals were lowered. The rapid return of the blood pressure to normotensive levels following potassium administration was associated with a return to normal of serum potassium levels. —C. R. SHUMAN

Effect of Weight Reduction on Normal and Raised Blood Pressures in Obesity. L. Martin. *Lancet* 2: 1051, 1952.

There is abundant evidence that people who are overweight have higher average blood pressures than those whose weight is normal. Experience has also shown that obese hypertensives are subjectively improved by weight reduction. This author studied the question of the fall in blood pressure in hypertensive obese patients who have lost weight. Thirty-seven subjects were studied, 18 of whom were normotensives and 19 hypertensives. None of the patients had chronic nephritis, malignant hypertension, or valvular heart disease. They had all been on a reducing diet and lost at least 14 lb. during the previous six months. Seventeen patients received 5 mg. amphetamine twice a day. Patients were seen monthly and blood pressures were determined under standardized conditions.

There was a statistically significant regression of systolic blood pressure amounting to about 3.5 mm. Hg for each 10 lb. of weight lost. Individuals who showed the most significant falls in pressure in response to dieting did not have any characteristics upon which such a response could be predicted in other cases. The effect of weight reduction on blood pressure in hypertensives is inconsistent and unpredictable. The chance of an occasional success, together with subjective improvement in the majority of patients, appears to justify the continuation of this regime as a routine measure.—S. O. WAIFE

Calories—A Limiting Factor in the Growth of Children. I. G. Macy. *J. Nutrition* 45: 189, 1951.

Physical growth is defined as a series of anatomic and physiologic changes taking place with increasing age from prenatal life through infancy, childhood, and adulthood. It is considered in terms of both visible and invisible growth. Increase of body dimensions or their anatomic changes and body weight are visible and subject to direct measurement. Invisible growth, on the other hand, may occur with progressive maturation and may be increased indirectly by absorption and storage in the body of structural and fundamental constituents obtained from food eaten, as revealed by basal metabolic rate determinations, or by roentgenographic recordings.

Values illustrating pertinent aspects of the relation of caloric intake to growth were selected from a comprehensive investigation of both visible and invisible growth of a group of children during a period of about 15 years. The values demonstrate: Wide variation in the growth progress of the same child at different times and of different children at the same time. Appetite may not be relied upon to insure ingestion of a good mixed diet which will furnish sufficient calories for satisfactory weight gains. The existing "standards" may not be depended upon in every case as criteria of dietary adequacy. There is a depression of nitrogen retention when intake of calories is insufficient to permit proper gain in body weight. Invisible growth may occur, as evidenced by nitrogen retention, coincident with failure of body gains—or even with loss of body weight. A difference in intake of as few as 10 cal./Kg. of body weight may spell success or failure in making satisfactory progress in visible and invisible growth.—B. SURE

Clinical Studies on the Use of an Oral Fat Emulsion. M. Shoshkes. *Ann. New York Acad. Sc.* 56: 22, 1952.

There is a need for supplying a large amount of calories in a relatively small bulk in many patients with chronic illness. Recently a number of palatable oral fat emulsions have been prepared. In this report the author describes his experiences with a preparation containing 40 per cent peanut oil, 10 per cent sucrose or dextrose in water, 2 per cent purified soybean phosphatide, and 0.2 per cent of a synthetic emulsifier, and small amounts of flavoring agents and preservatives. The caloric value was 4 cal./ml. The emulsion flowed freely even in the cold and could be easily administered by glass, tube, or nipple feeding. It remained stable at room temperature for 6 months.

About 75 per cent of the 141 undernourished subjects, some with and some without an active illness, could easily tolerate the mixture by mouth. The average weight gain over a long period of observation was 0.2 lb./day for an average ingestion of 0.1 lb. fat per day.

Five subjects with active peptic ulcers did particularly well on the mixture, but patients with subtotal gastrectomies or with steatorrhea due to pancreatic deficiency did not tolerate the emulsion satisfactorily.

It would seem that oral fat emulsions, as well as parenteral preparations, will be in general use in the very near future. The immediate problems relate to dosage, palatability, and technical improvements.—S. O. WAIFE